Science AMA Series: We are researchers at Johns Hopkins University's Institute for Computational Medicine, Feilim Mac Gabhann and Sridevi (Sri) Sarma. We use computational methods to improve therapies

ComputerMedicine [1] and r/Science AMAs[1]

[1]Affiliation not available

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Hello and thank you for doing the AMA!

As a young computer science undergrad with a keen interest in science and a couple minors in physics and bio, I have always been wondering how people manage to take CS and turn it into a research career in your area.

What should a person in my position do in order to get to do work in your field? Do I continue as soon as possible into the natural sciences? Do I get a PhD in CS, but work on a related project? What should I be working towards, academically as well as in ways of hobbies and employment, in order to become a researcher in this field?

Or, perhaps to phrase it less openly, how did you get into your current field? How did your colleagues?

timipeko

[FMG] My main advice to you is to work really hard on the biology and/or physiology - whatever part of biology interests you the most. Building models, and writing super efficient code, is helpful, but means little if it is not being used in the service of answering real biological questions. Think of the code as the tool rather than the end result; the code or the model is our window into the biological mechanism, in the same way cell culture can be an experimentalist's window into physiology or a mouse is a window into human biology. The biology comes first.

That said, there is no reason that you can't do all of that during a CS PhD. It's not about the initials on your degree, it's about what you actually do in your work - that's what defines what you are and how you get to where you want to be.

For myself, my undergraduate was Chemical Engineering at University College Dublin; then I came to JHU to do a PhD in Biomedical Engineering and fell in love with molecular biology, it just 'clicked' in my head (I hadn't done biology since I was 15). So now, I work on molecular biology with a chemical engineering mindset, and that makes me a systems pharmacologist. Follow your own path - there is no right or wrong way to get where you want to go!

Last thing - I'll also say that I was writing code from the age of 11 (shout out for learning BASIC on a

Spectrum 48K!) and I've never stopped coding since, even through a stint as a management consultant.

Hi there!

So, despite sometimes using them at work, I'm always super skeptical of "big data" analysis. I always feel that, without a strong underlying already known model, correlating signals isn't going to give us any kind of useful information, or at times even providing numerically correct results at all.

Could you shed some lights on some analysis techniques that ended up translating from the computing lab to the development of an actual "thing" that could be observed in vivo? (e.g.: related to connectomics in EEG/fMRI, genomics and things like that)

(I hope that my question is clear enough, I didn't go into details of a specific case because I believe that it's a general issue. But I get that my post might be a bit confusing)

lucaxx85

[SS] Correlations are tricky – at least interpreting them can be. I think it is useful to use correlation analyses to detect trends in data. However, what you infer from your analyses can be completely misleading. For example, a common error in neuroscience is to mistake correlations with causation. You simply can't tell if one variables causes another variable to take on some particular values. You need more information than time series data. You need to know (in the neuro example) if one brain region projects to another to then possibly infer causality.

With this said, sometimes statistics themselves may not necessarily translate to something observed in vivo, but can be useful in translating to the clinic. For example, we are working on developing a tool that assists neurologists in finding the seizure onset zone (SOZ)(region starting the seizure) of patients with focal intractable epilepsy (seizures cannot be controlled with drugs). The tool processes invasive intracranial EEG signals to generate predictions on which brain regions may be near the SOZ. The predictions are solely based on patterns seen in network-based statistics (pair-wise correlations between pairwise EEG signals in fact). The tool has been proven to be effective in predicting treatment outcome when tested in a retrospective study including 42 patients. Now, it is being tested in 3 epilepsy centers...so bottom line..I do think correlation analyses are useful...but be careful what you infer from them.

Hi there!

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lucaxx85

[FMG] Studying big data directly - analyzing through bioinformatics, machine learning, and other techniques - has yielded some great results, including diagnostic and prognostic products that are already used in the clinic. These approaches mostly focus on identifying the 'signal' from noisy high-

dimensional data. (In this case 'high-dimensional' means that lots and lots of measurements have been made of each patient). To greatly oversimplify, the idea is that by measuring enough different things (genes, proteins, ...), we will find the metrics that will predict who will respond well to drugs, and be able to differentiate them from those who will not.

Recently, there has been a large shift towards marrying the big data with detailed mechanistic models. In essence, bringing back in decades of hard-won experimental data to help us understand what all that big data is really telling us.

For too long, we have had researchers focused on the 'micro' - the mechanisms, and other researchers focused on the 'macro' - the system-wide quantification of as much as possible, and these worlds have been separate. Now, these worlds are coming together and that's really what we need to understand these really, really, complex systems. It's very exciting, and gives us a much better chance to affect patient clinical care.

Hi docs!

Big Data analysis is known to work effectively in industrial machinery as they are predictable and conform to standards. However, humans are not mechanistic and every human's physiology is unique. Given all that, how do you make a reliable model for the interpretation of the obtained molecular level data to translate it into life size results?

Also, what are some of the factors which came up in your research that cause common medicines to be effective for some and ineffective for others?

aurobindodharsaun

FMG] It is true that we are all different. However, we have many things in common, and the differences are more quantitative than qualitative. What I mean by this is that we (almost) all have the same genes, proteins, etc, but each of us will have them in a different quantities. At the physiological level, each of us has muscles but some people have larger/stronger muscles. So the differences are more in terms of number. That means that we can build models of people that are similar, but the numbers are different. Then our challenge is to measure these differences.

Basically, we're all made of the same materials but in slightly different amounts; if we can measure those differences (and, increasingly, we can) then we can hope to identify why those differences cause (for example) a drug to work for one person and not another.

As to getting reliable models, the key is validation. We need to test and test and test again, challenging our models to be predictive in new situations.

Examples of factors from our research that affect medicine efficacy: how much of the drug's target protein there is (obvious); how much of a select set of non-target proteins there are (less obvious), even when these proteins are in completely different tissues (even less obvious); and how much exercise the patient gets (quite surprising). This shows how integrating physiology with molecular biology can give us some intriguing and complex answers.

You mentioned that you build computational and statistical models of electrical activity in neural circuits

Do you think that within the next 20-30 years, these models can become accurate enough that synthetic brains (whether mimicked through circuitry or modeled with neurons) can be made?

MonteDoa

[SS] There already exist many big initiatives to create the virtual brain (e.g. http://thevirtualbrain.org/tvb/zwei, or http://bluebrain.epfl.ch). And other projects that try to replicate a particular system, such as the visual system (a renowned researcher in this field: http://cbmm.mit.edu/about/people/poggio). They can compute and simulate neuronal activity, but they don't model the link to behaviors. Simulating brain activity is great (especially when trying to understand neural patterns in health versus in disease), but we are far from the Terminator if these brains don't generate behavior.

I am studying library and information sciences and am fascinated by bibliometrics. Your research reminds me of this. Although the data you have to consider is far beyond just a text or journal. How do you collect all this data? Who indexes it so it can be properly analyzed? How much time is invested in a single study?

How do you decide what data is important to collect from a medicated patient/treatment trails, versus what not to collect? Could you possibly give some examples of the data you collect?

Never-Created

[FMG] How do we collect this data? With lots and lots of help! In most cases, we are not the people collecting the data. The scientific field is very good at collecting data - it's what most researchers do every day - and fairly good at sharing data (there are major initiatives at the NIH and elsewhere to further improve sharing, openness and transparency, they are worth looking up).

Our role is to use computational models to better understand this data, including but not limited to, how to resolve disagreements between data sources, how to combine different data sources into a coherent framework, and then (most importantly) how to harness that data to build predictive models that would be useful to other researchers or physicians.

To your other question - ideally we would collect as much data as possible, but this is not always feasible. Right now our models could be greatly improved by having more serial data from patients, i.e. the same measurements over time. But these measurements are often invasive, so that's problematic. We and others think that this dynamic data will ultimately be more revealing than measuring everything about a person at their first doctor's visit/biopsy and not revisiting that data. A snapshot tells us less than a movie!

Lastly, we use our models to tell us which components are more important to 'get right' - some elements of a model don't affect the outcome, while others are crucial. This is generically called a 'sensitivity analysis' and there are many many types. Using them well can help the models drive the experiments, and continue the 'virtuous cycle' of model and experiment.

Which technicals skills are best to have in your work? Like which programming languages you need to master, and on what do you need to be most knowledgeablea about (statistics, databases, chemistry, molecular biology, genetics, genetic libraries, etc.)?

DutchBionaut

[FMG] You have a great list started there!

In terms of coding, and anything really, we match the skill/tool to the problem. In our lab, different people use different tools at different times. Matlab, Fortran, R, Python...

As I mentioned in another answer, I think the most important thing is to deeply, deeply, understand the biology and physiology of the problem. Of course, there is almost no end to the complexity of biology,

and it continues to emerge, so we must keep up, but without an appreciation for the biology then we would be lost.

Which technicals skills are best to have in your work? Like which programming languages you need to master, and on what do you need to be most knowledgeablea about (statistics, databases, chemistry, molecular biology, genetics, genetic libraries, etc.)?

DutchBionaut

[SS] In my lab, students are proficient in MATLAB (or Python), statistics, dynamical systems and control, computational neuroscience.

Hi professors! Former student of both of yours here. I just wanted to ask what your thoughts are on the value of undergraduate research and how institutions/faculty can balance their research goals with their educational ones. At a place like Hopkins, I've found that oftentimes one gets prioritized over the other, and ultimately the interests of either the students or the institution are compromised. Thanks for doing this!

guitard00d123

[FMG] Great to hear from a former student! Come say hi next time you're in Baltimore! Undergraduate research is one the best experiences a student can have. It gives them an opportunity to be creative, to take ownership of a real-world project, to work in teams, to have close contact with faculty... the list of positives is endless. From the faculty side, the opportunity to work with some of the smartest students around is very rewarding, most of us really look forward to having undergraduates in our lab.

I strongly believe that we are the sum of our experiences and interests, at least of the ones we enjoyed; so I would love to see students have more time to spent on cultivating their unique interests (research, design, or other university clubs). Classes are important, but these other experiences can do more to shape us and help us find direction.

My undergraduate experience was very different - no homework and no midterms. It left us a lot of time for non-class experiences. Obviously that was a different country and a different time, but I think you see a movement here at JHU and in other places to move away from overly prescriptive/narrow class assignments and towards more project-based classes that bring a more research-like experience into the classroom. I think this aids both learning/retention and creativity, we'll probably see much more of it over time. These assignments are harder to grade but much more enjoyable for student and faculty alike!

As someone who is interested in computational medicine/neuroscience with a neuroscience background but less experience in programming and math---what resources would you recommend to learning the subject?

Maqool

[SS] Computational neuroscience often is associated with the field of describing neuronal firing patterns with mechanistic (biophysical-based) models. Thus, the models take into account the mechanisms of action that cause a neuron to spike (ion concentrations inside and outside the cell, voltage-gated ion channels on cell membrane etc.). To understand such models, it is very useful to understand Dynamical Systems Theory and Nonlinear dynamical systems. If you are interested in manipulating and controlling neuronal systems (say in simulation), then a course on Systems and

Controls is useful. Many universities offer these courses online (e.g. http://ocw.mit.edu/courses/electrical-engineering-and-computer-science/6-241j-dynamic-systems-and-control-spring-2011/)

You referred to your work with drug therapy as "virtual clinical trials." Has any of your work been validated against actual clinical trials? Also, considering the differences in drug metabolism and efficacy across different patient populations (eg: European, African, Asian, etc), which patient population are your virtual trials designed to simulate?

C8H9NO2

[FMG] I've never been asked a question by paracetamol before - nice user name. Yes, we validate our work as much as is possible. With clinical trials, we are able to compare to any publicly-available trial datasets, or datasets held by collaborators. However, clinical trials do have a special difficulty in that much of the most recent data is held by private pharmaceutical companies. We and many others are working towards improving access to this data and many pharmaceutical companies are opening up to the concept of sharing and/or collaborating on this data.

I will say that with a strong validated foundation (which is truly key), our virtual clinical trials can then hope to go even further. We can run virtual trials that would be prohibitively expensive, impractical, or just plain impossible for a real trial. Some examples: we can simulate different treatments in the same set of patents; we can simulate every dose, schedule, and combination; and we can simulate hypothetical drugs (as well as real ones!) to identify what functionality an ideal or improved drug would have.

Lastly, remember that for the foreseeable future all virtual clinical trials are upstream of real world trials. The goal is really to narrow the set of possible treatments, or identify the best trial populations, so that the clinical trials themselves can be as efficient as possible.

Thanks for doing this! Where do you get your datasets for treatment responses? If it's medical records or claims data (eg all of Kaiser's patients, all of Aetna's patients), do think it's biased towards older and cheaper treatments? Or at least that more can be said confidently about older and cheaper treatments? My concern with those datasets is that drug/treatments that came out in the past few years would likely only be used in a small subset of the population because insurance forces people to try numerous older drugs first. The people receiving the newer treatments are likely refractory cases or extra sensitive to side effects, further biasing the assessment of the latest treatments.

prettywitty

[FMG] You are correct that every dataset can have some inherent biases. A dataset unintentionally enriched in a certain type of group of patient can be really informative though; the main thing is to know what the composition is. We always need to be aware of what the characteristics of the patients in our datasets are. If we want our models to be truly predictive, that is, to predict the outcomes for new patients that were not used to build or calibrate the model, then we need this information.

I don't personally work with HMO-style data, but I think your reasoning is sound! In real clinical trials there is a related effect: often the trial is run in the most sick, most refractory, worst-outcome patients, which can mask benefits that could be obtained by patients at an earlier stage of the disease. All diseases are dynamic; treating on day 1 is not the same as treating on day 100.

My answer to C8H9NO2 (nice) above has some additional relevant info on where we get datasets, both public and private.

what is the difference between biostatistics, bioinformatics, and biomathematics?

Boobs911

[SS] Biostatistics is the field of finding patterns in data generated from biological systems. Sometimes the statistics just show trends (one variable increases while another decreases) or elucidate how information is encoded in the biological system (a motor neuron's firing rate correlates to the direction of movement of the subject). The latter, studying information in systems (biological or not), is the field of informatics and applied broadly to any information processing systems. I have never heard the term biomathematics, but I am assuming it is synonymous with Computational biology, which is the field of describing biological systems with mathematical equations derived typically from natural laws.

Seems to me that >90% of illnesses could be diagnosed by computer software. At Rite Aid (or the like) the computer asks about your symptoms and takes your temperature, just as a physician would. It then calls for certain blood and urine tests done on the spot. It then either offers a diagnosis and medication, or instructs you to see a physician. Followup is mandatory. If you fail to report daily until closure, you must pay a penalty next time. (This is how the diagnostic program steadily improves itself.)

moore40

[SS] I am not sure where you get the 90% figure, but it is true that many ailments get diagnosed via predictive models or formulas. Sometimes, these models are very robust, and sometimes they are not computed quickly enough (e.g. scoring for SEPSIS or SEPTIC SHOCK in the ICU) to effectively treat the patient.

Seems to me that >90% of illnesses could be diagnosed by computer software. At Rite Aid (or the like) the computer asks about your symptoms and takes your temperature, just as a physician would. It then calls for certain blood and urine tests done on the spot. It then either offers a diagnosis and medication, or instructs you to see a physician. Followup is mandatory. If you fail to report daily until closure, you must pay a penalty next time. (This is how the diagnostic program steadily improves itself.)

moore40

[FMG] As regards your estimate of 90%, I will say that Diagnosis, Prognosis, and Prediction of Drug Response are all important, and Computational Medicine has a role to play in all three. There is just as much or more to be gained from improving prevention as improving treatment.

I will say that something we think about a lot is how to position algorithms between doctors and patients. Many doctors have years of experience that can benefit the patient in unforeseen ways. In addition, doctors may not want to be simply pushing a button to get the best answer for how to treat. There is likely a happy medium where algorithms serve as physician decision support, as opposed to an automated dosing system.

Computational methods are promising and we all stand on the shoulders of scientists like yourselves. Can you comment on how useful large scale virtual clinical trials are in practice? Also can you give an example of how improved diagnosis of sleeping disorders can aid physicians in treating the various subtypes of sleeping disorders?

doctoraus

[SS] Despite the prevalence of sleeping disorders, there does not exist a real objective means to diagnose many of them (e.g. insomnia). At present, the gold standard for discriminating between a patient suffering from a sleep disorder and a healthy sleeper is through clinical interview and the use of screening tools such as the Pittsburgh Sleep Quality Index (PSQI) which assess sleep quality and disturbance based on series of standardized questions.

A promising alternative to the questionnaire that is already being used by clinicians is the polysomnography (PSG) which represents the sleep fields' gold standard for measuring and monitoring overall sleep architecture. The EEG data is scored in a laborious and subjective process by sleep specialists who assign a sleep stage to every 30 second intervals of the EEG data. This scoring process costs $400-$600 per patient, and the clinicians then make a diagnosis based on the annotated data. The standard procedure is currently heavily dependent upon human factors, and at the end of the day, the most commonly used PSG-derived sleep features (e.g. total sleep time, latency to persistent sleep, wake after sleep onset, and sleep efficiency) as well as more sophisticated spectral-based features do not discriminate between ”good” and ”bad” sleepers. Thus, there is a great need for an enhanced interpretative approach for PSG that is inexpensive, provides a valid biomarker for specific insomnia and other sleeping disorders, has prognostic utility, and is modifiable based on disease treatments and clinical symptoms. Such markers can be found through sophisticated data analyses and may be much more specific to subtypes of sleep disorders.

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doctoraus

[FMG] Computational methods for personalized medicine really break down into two major applications: (1) Virtual clinical trials that allow us to simulate a treatment on thousands of virtual patients (typically based on real patient data); and (2) precision medicine trials ('n-of-1 trials') in which we are simulating every possible treatment for one specific person.

I think that the first type is more likely to see utility first, and is already in use by many pharmaceutical companies. Some of the first drugs designed based on computational models are in late stage testing now (I was not involved with these, they were developed at private firms). Being able to have an impact on drug development waaaaay upstream before the clinical trials begin has huge economic and therapeutic potential. Only 7% of oncologic drugs make it through clinical trials to the market, and the reason drugs cost so much is that the patients are paying for the 11 out of 12 drugs that failed. So anything we can do to improve these odds, or prevent people getting drugs that won't work for them, will be have great impact.

The second type is much more difficult and will require much more validation, because then the model is being used in a true clinical setting. We might see algorithms being tested for approval by the FDA in the way that drugs are.

As the big data tool becomes more ubiquitous, what resources do you recommend to other researchers so that they may better understand, critically appraise, and potentially contribute to such projects? Thank you!

x_plorer2

[SS] To contribute to projects in the field of computational medicine, you really need a solid handle on

the biological system you are studying as well as the computational tools that will be useful. The future in CM research will not be about having a suite of tools available for the research to study a system, but will be about how to develop creative relevant models to answer the question of interest. This required deep expertise in the biology and in computation.

Thank you for doing this AMA.

I suffer from sleep apnea. In fact, I had my tonsils and adenoids removed as a way of reducing the severity of it, and improve my quality of sleep.

Is the underlying cause of sleep apnea purely mechanical, as I have been led to believe, or is there a neurological factor at play as well?

theclarinetsoloist

[SS] I am not a clinician or expert on sleep apnea unfortunately. But, my collaborators at JHMI are wonderful and I encourage you to try to speak with them: Drs Rachel Salas and Charlene Gemaldo. Best of luck.

Hey guys, thanks for doing this AMA. As someone who's trying to enter the field of bioinformatics/computational bio and is really interested in the research you guys are doing, do you have any tips for an undergrad biochemistry major? Also, how can (if it can) computational biology and bioinformatics be applied to things such as gene therapy and drug delivery (along the lines of targeted delivery vehicles)?

Prot00ls

[FMG] OK, I say this as someone who came from non-bio computational field (Chemical Engineering) into biology: I think coming from bio/biochem into the computational side is potentialy even more promising than going the other way. I say this because I think that the biology and biochemistry has to inform the models before the models can inform the biology. So if you are interested - just go do it!

Tips for a biochem major: get comfortable with numbers... take every differential equations, statistics, and/or programming course you can. Take every opportunity you can in those courses to apply them to a biology or biochemistry question. If there are computational research labs where you are, join one. If not, go do a summer internship at one.

Lastly, there really is no limit to the types of therapeutics that can be studied using these models. We have developed models of drug delivery, gene therapy including targeted vectors, liposomes, cell-based therapy, bone marrow transplant, exercise, ... just about every type of therapy you can imagine.

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Prot00ls

[SS] At JHU, we have a new undergraduate minor in computational medicine (CM) for students in the schools of engineering and arts & sciences. So, for a biochemistry major such as yourself, we have a training program to prepare you for CM research. The program would recommend appropriate math,

statistics, and computing courses that you would need to take to enter. Then, as part of the program, we offer two introductory courses in computational medicine that cover fields and applications of computational physiological medicine, computational anatomy, computational healthcare, and computational molecular medicine. In these courses, we divide the class into teams and give them projects in each field over the year. Students apply their computational training to solve real problems in CM - which exposes them to data and models. So-as for advice-if your school does not offer such a program, perhaps take a look at the coursework offered by our CM minor (http://icm.jhu.edu/academics/undergraduate-minor/) to guide your plans. Good luck!

One question md/phd students always have is where we can fit in the current medical and research environments. Computational medicine seems like a expanding, new niche that can be a perfect intersection of the two training programs. What role do you see physician scientists playing in computational medicine, and which fields (or residencies) do you feel are closest or farthest from incorporating large scale -omic data in the clinic?

terpaholic12

[SS] I believe that the medicine of tomorrow is computational and personalized medicine - synonymous perhaps with evidence-based medicine. This means, I think that Drs of tomorrow will be understanding, developing, and using mathematical predictive models to help them diagnose and treat patients. Which means, that they should acquire the appropriate training to be part of our future! MD/PhDs should absolutely receiving an education in computational medicine and more importantly contributing to the educational components of this relatively new field. We need clinicians teaching our youth what problems can be effectively solved using models, not mathematicians telling clinicians what they want to solve. Currently, the Institute for Computation Medicine at JHU (www.icm.jhu.edu) consists of faculty that are primarily mathematicians, engineers, and computer scientists. We need more clinicians to participate more in education of comp med.

Hi! Thank you for your work! Have you explored how therapies such as EMDR, CBT, Neurofeedback, acupuncture, Reiki, etc. effect the electrical activity in the brain? Studies in cancer patients receiving one or more of these therapies show a significant increase in pain relief and emotional comfort. This is the best state for healing to take place. How do you include the variable of the human spirit and will in the healing process? Thanks so much!

illuminatedowl

[SS] Chronic pain is a new research thrust of my lab. Indeed we are developing mechanistic models of the spinal cord networks to understand the first processing station of pain signals. Although we began the project by trying to understand the mechanisms of action of spinal cord stimulation (SCS) for chronic pain, we are also investigating, in both computational and mice models, the effects of various tactile stimulation (e.g. acupuncture) and alternative methods. NIH has a National Center for Complementary and Integrative Health (NCCIH) that looks into such alternative approaches and integrative approaches that you mention. Take a look at their website!

How can you computationally predict the efficacy of a drug when the individual human brain chemistry varies. Age, genetics, environment, culture etc... Seems a bit ambiguous. However, I would much rather the see neural stimulation research being pulled out of the well instead of "smart drugs". Keep it up.

Fatmansherb

[ss] Personalized models are becoming more and more popular, and are more robust when considering the person to be a “cohort”. I don’t personally research drugs. However, I agree with you. Electrical stimulation of the nervous system has several advantages: it’s reversible, has fewer side effects (as long as you don’t create bad side effects by stimulating the wrong circuits!), and we are beginning to better understand its mechanisms of action on the nervous system.

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Fatmansherb

[FMG] See my response to aurobindodharsaun above; short version: we are all different, but more in terms of quantity than quality. There are of course specific genetic differences that can rewire how our proteins interact with each other; but for the most part our differences are a matter of degree (I might have more of protein A, you have more of protein B, ...).

This gives us hope that by measuring the differences we can understand human variation in a common framework.

Hi,

Thanks for doing this AMA. Just out of interest, are distributed computing initiatives such as World Community Grid or SETI still necessary in the age of comparatively cheap big iron?

snarkenfudel

[FMG] Most of our models, even complex ones, are so fast that we could run thousands of different drug trials on a doctor's laptop while they are talking to a patient. That's not me bragging, that's just how fast computers are now. This is important because it suggests we could have a frictionless physician assistance role, helping doctors identify which courses of treatment might be best for each individual, without 'sending away for results'. Point-of-care algorithms could be transformative.

At the same time, we also build some models that take a long time to run... especially those were we simulate the body or select organs in three-dimensional detail. We will continue to find more and more complex problems that need lots of computing power, so I'd doubt that distributed computing is going away soon.

Do you deal with resistance from others in your field to your computational methodologies? Eg. Do you encounter other scientists who effectively say, "theres no way to understand your complicated code, and it probably has bugs we don't know about, so it can't be useful," or some variation? How do you address that if so?

awesome_shtein

[SS] Yes. As a control theorist by training, I am often taking a reductionsit point of view on complex nonlinear networked systems. Therefore, we ignore some details that are no as relevant to the questions we are trying to answer. This bothers many biologists in particular, as they want “realism” in their models. My view is that detailed biophysical models have their important uses: testing hypothesis using simulation, prediction, etc. However, if you are trying to say perform sensitivity analysis to see which parameters are sensitive to specific inputs, then a large detailed model is less tractable and a

reduced model may be more appropriate.

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awesome_shtein

[FMG] Oh yes. When I was at the University of Virginia, Brian Duling used to challenge me daily on this subject. He claimed not to believe that these models could tell us anything new. He unfortunately passed away not too long ago, but I really enjoyed sparring with him on this. To this day I'm not sure whether he really believed it, or just really enjoyed the arguments :)

I haven't experienced the 'bugs' comment you suggest, but a more common critique is that since experimental data is needed to build the model, then it can't tell us anything that we don't already know. This simply isn't true. Models are a window into the system. We wouldn't suggest that human cells in a dish, can't tell us new things about human biology; instead they allow us to explore human biology in a new way. It's the same with models... and with the emergence of big data and its identification of just how different we are from each other, and even how different each of our cells are from each of our other cells, we will be truly lost without detailed, mechanism-based, biophysically-accurate, predictive models!

I have had some thoughts recently about conducting medical research into curing non-human carriers of human diseases. My beliefs would be that methodologies not ethically usable on humans could be used on these carrier-patients. I.e. finding a way to cure mosquitoes of carrying malaria would also cure (or all but) malaria in humans.

Generally, does this kind of "lateral step-around" (of ethical concerns of direct human testing) research happen already? If so, by whom?

What would be needed to use your assets, technological methods, and expertise to attempt these "virtual studies" in non-human life forms?

Do your methods help study drug combinations, or are they still only single drug 'trials'?

MainAccount

[FMG] I teach a class in the Ethics of Biomedical Engineering Innovation. We just finished a module on just these kinds of interventions. This fall I'll be co-leading a new class, Practical Ethics for Future Leaders, that will again focus on some of the same themes.

I would look up "gene drives" as a starting point - some versions of this suggest eliminating the disease-causing mosquito species, but others suggest making the mosquito incapable of carrying the disease.

What's need to attempt these studies - time and expertise. The more people that build expertise, the more time Science will have to dedicate to these virtual studies.

We definitely look at combinations. We typically study single drugs first, because that's where most data is available for validation. Once validated, we test combinations.

What is your primary method of commercializing your discoveries? Are there companies actively using your research for commercial activities?

uber_neutrino

[SS] I have only done this once (and it is happening now!). We went from interesting results from a research study to (i) filing a patent on the idea/method, (ii) applying for funds available only to JHU faculty [often easier to get than perhaps external funding agencies but typically less $$], (iii) completing retrospective study to test the validity of the method in the clinic, (iv) applying for more funds to hire a developer, (v) hire the developer and create a prototype ready to be installed in the clinic, (vi) obtaining permission to conduct a prospective study in the clinic (IRB), (vii) gaining clinical validation as doctors use tool....In the middle of those 7 steps, I incorporated a company, recruited a board of advisors (Experts in the field), and started talking to potential partnering companies. As of yet-no companies are using the tool - as they are waiting to see what the clinicians say!

In your opinions, what is the future of computational medicine?

teambeyonce

[SS] Hi Ladies! YOU are the future of computational medicine. You are the new generation of engineers and scientists who are learning how to mathematically model biological systems in health and in disease to discover new therapies. Some of you may move on to med school, and you will be the first doctors of our future as you will use quantitative methods and data to help you treat your patients more effectively. We have lots of technology that allow us to gather data from patients (physiological data etc), what we do not have are doctors who can intelligently use that data beyond what their brilliant minds can process mentally. The past is doctors relying on experience to develop mental models of disease. The future is to combine this with predictive models.

What sort of pathways exist into this field for software developers with plenty of experience in the technology sector, but no background (academic or otherwise) in medicine or biology?

mrynx

[FMG] This is for MystJake too... All I can say is, just start now. Read voraciously, take online courses, and find out what is available locally. I used to be a management consultant, writing presentations on supply chain logistics. Then I went back to school, took courses on molecular biology, took courses on human physiology, ... and I just kept going. One of our computational biology professors here had previous career as a nuclear physicist. The journey of a thousand miles and all that. Good luck! Learning more is always, always worth it!

This is for professor Gabhann.

From what I understand, you are creating a separate model for each drug treatment that predicts success based on variables collected prior to treatment. Are the 'virtual clinical trials' then just matching which treatment would be best for each patient based on which treatments model gave the highest success rate?

What sort of variables do you have to work with to predict success? Do you have a way of determining severity of the diagnoses? (if only you had a control group with no treatments)

123jason2

[FMG] No, we don't create a different model for each treatment. We create a model of the drug targets and all their known associates (this typically means the disease-causing protein and any proteins that interact with it or compete with it). We make sure that this molecular/cellular system is within a model of real human (or mouse, if that's what we're looking at) physiology. Then, we can bring any number of different drugs into the model that target different components of the network that we've built.

Rather than just predicting the outcomes of already-run trials, we want to identify the mechanisms or biomarkers that cause this to be so. The reason is that only knowing the mechanism will allow the model to be predictive once you move into different patients. Just being able to recreate which patients lived is not useful unless you can identify why.

Variables: typically we work with gene and protein expression data. That's already a lot of data, but more can be included - phosphoproteomics, physiological data, disease/drug history, and more.

What mathematical models do you use? Dose-response curves? Machine learning methods?

What do you use to model the data? Excel? R? Matlab?

It looks like I have a good background in what you guys do (disease research/diagnostics, drug delivery, dose-response, computational methods, optimization, modeling, ML, brain scans, programming). Let me know if there's anything I can do to contribute.

Batmantosh

[SS] All of the above :). Really, the models all depend on what you are studying. In my lab, we sometime used biophysical based models that describe interacting mechanisms leading to qualitative patterns of neural spiking. These can be complicated coupled nonlinear ODEs with many unknown parameters, but are "realistic" and interpretable. We also use statistical models, which capture the structure of, or predict the precise timing of spikes as a function of the biological/behavioral signals represented in the brain. Such models treat the neuron as a black box, looking for associations rather than mechanisms. Both have their uses depending on the question you are after. We also use MATLAB to estimate and run our models.

Hi! Thank you for doing this AMA Do you think computational medicine will become a common tool for patient specific treatment in the future? I mean will its cost/complexity be reduced as to be used by health care professionals everywhere?

MarcoMalaga

[SS] Yes! I do think computational medicine (CM) is the approach of the future. You highlight an important use of CM - to develop models and tools that can be used by professionals (or non-professionals) everywhere. Consider a developing country that cannot effectively monitor critical care patients (not enough clinicians and experts around 24-7). We can have computer algorithms monitor the patients instead. We can come up with algorithms that process physiological data gathered from say low-cost devices, and detect when a patient may be slipping into an adverse clinical state. An alarm can then be sent to an appropriate professional, or the patient can seek help.

Hi Drs. Sarma and Mac Gabhann! We have another question. What the most poignant experience you've had in your field?

teambeyonce

[SS] Let me share an awful experience that I had in graduate school so that you understand that everyone's career path entails successes and failures...I was told at the early stages of my phd that I wasn't cut out for research. A very famous professor said this to me and I was devastated. It initially broke me, but I slowly picked up the pieces and with great mentoring and great support from my family - I persevered and proved him seriously wrong! I wanted to throw my 13 faculty interviews (7 offers) in his face, but I had to be a grown up by then..after all I was about to start a career :) Bottom line - never give up..believe in yourself...keep supportive people close by...and do things that make you happy :) for me, that would be eating chocolate cake.

Good afternoon! Master's student in Applied Mathematics with a concentration in computational mathematics here -

Can you speak on different classes of problems that require different numerical algorithms: e.g. Cases in your research when you implement data mining/machine learning algorithms vs. numerical solvers for systems of ODEs. I am familiar with using classification algorithms to detect cancers; I've heard lectures using Runge-Kutta methods to solve problems like calcium transport.

What practical problems do you work with on a day-to-day basis? Thanks!

svrfvvax

[SS] Ok. When we want to understand the mechanisms of action of something - like deep brain stimulation applied to a neural structure, we use biophysical-based models that capture mechanisms of how spikes are generated in neurons and networks of neurons. On the other hand, when we want to understand how say neural patterns induce behavior, we use statistical models to derive a function that describes how behavior correlated neural spiking. This approach often involves data mining, machine learning etc. Also see my response above to Batmantosh...

Are you doing anything to work on Lyme disease?

VesperLynde

[SS] Sorry I am not.