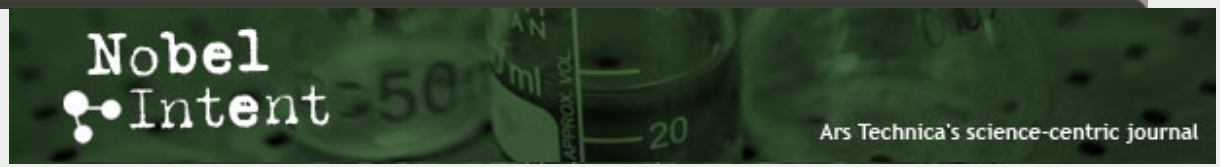


Modeling cells as porcupines

By Matt Ford | Published: November 07, 2006 - 04:16PM CT

I am sure many have heard the old physics joke regarding modeling a horse as a sphere to make the math easier, and while funny, it is often very true. In order to fully simulate a system accurately, you would need to get down and solve the quantum mechanical equations that define each and every atom in the system... This quickly becomes intractable, even in systems with a few electrons. This becomes exactly impossible when you start to discuss systems on the size of cells. So, in order to get around this, physicists (and engineers and mathematicians) come up with simplified models to make the math easier, but hopefully capture the important physics of the system. This brings to mind a quote posted* in my last simulation write up that is attributed to Prof. George E. P. Box:

> "All models are wrong, but some are useful."

Very, very true words. A model need not have every last detail included to be useful or to help us learn from it.

Recent work from the Max Planck Institute of Colloids and Interfaces in Potsdam and at the University of Heidelberg has illustrated this very nicely. Researchers there set out to study cell adhesion in blood vessels. Even with a lifetime of work, one can not fully model all the interactions that occur within a cell, or between a cell and the vessel wall. Instead they choose to use a simplified model of a cell, one that resembles a porcupine, to simulate this complex system. In the process, they identified what are key parameters for cellular adhesion.

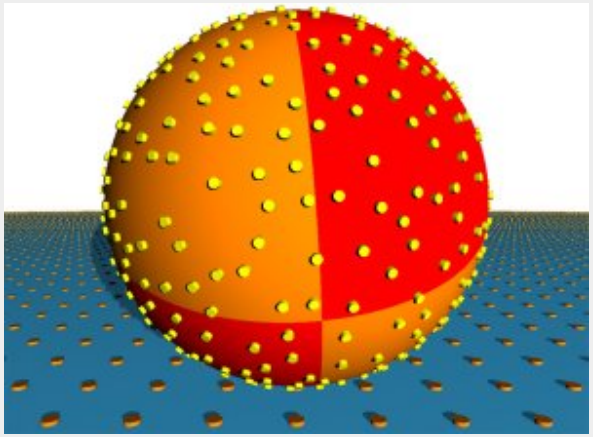
From the Journals

Bully coming to the Nintendo Wii, Xbox 360

The "controversial" Bully may find a new life on the 360 and Wii, as new versions of the game come out this winter.

+ READ MORE

Blood is the highway system of our bodies: it transports cells throughout the body via hydrodynamic forces resulting from our pumping heart. But these forces do not tell a cell where to exit; this is left to specific groups of specialized molecules called receptors that exist on the cellular surface. Receptor molecules work on a lock-and-key principle, e.g. the receptors on a certain cell will only fit into the receptors on its destination tissue, which ensures that the cell ends up where needed. The research team sought to understand what is most important physics in this process, what is it that causes cells to stick? This sticking process is critical in many biological applications. Malaria-infected red blood cells will stick to vessel walls to avoid destruction by the spleen, and white blood cells attach themselves at certain points to help fight off foreign bodies in adjacent tissues; therefore understanding the underlying physical mechanism is an important first step in exploiting it to our advantage.



By modeling the cell as a sphere with sticky knobs randomly placed on its surface, and the tissue as a plane with an even arrangement of similar sticky knobs, the researchers modeled the hydrodynamic flow of cells passing over this surface to see what stuck. It was found that higher flow lead to a higher number of cells sticking to the surface, since the increased flow would allow them to find a matching receptor on the surface more quickly. They found that increasing the receptor density on the cell itself increased the adhesion, but only to a point. The team found that beyond a few hundred receptors per cell, there was little gain in adhesion; this was because the receptor's effective areas would overlap each other due to the random thermal vibrations present in the system. Similar results were seen in the when the size of the adhesion areas was increased for similar reasons.

What was found to have a surprising effect on the adhesive properties was the *height* of the receptor knobs. The simulations showed that cells would have a large increase in adhesion rate from only a small increase in the height of the knobs. This phenomena is seen in nature as well: both white blood cells and malaria use this "porcupine spine" mechanism. What the researchers discovered is that this may not be limited to just a few systems, but rather is a feature of many other biological systems that exhibit similar behavior. This works emphasizes a point I made in a earlier article—we are living in interesting times, where experiments and simulations are now looking at the same thing, each bringing new information to light and helping advance science even more. No longer do advances in computational chemistry|biology|material science|engineering mean a trivial bit of information, but a real step forward in our scientific understanding of a system. This is just one of the latest examples of it.

*Thanks to rx_MD for posting Dr. Box's quote

Filed under: computer simulation, computational biology, medicine, Science

Recent Features

- Online backup solutions: a review
- The new E3: a postmortem
- At the races with the Kangaroo TV
- Broadband on the go: the ups and downs of Verizon's EV-DO network
- iPhone in depth: the Ars review

OpenForum

- Emergency Alert! A friend wants to spend $2700 on a Bose System
- Post your LOC
- N00bs new build won't power on at all. *Totally Lost*
- Microsoft CY07Q2 Results are in
- Renting Microsoft Office 2007

Editor's Choice

- Copyright coalition: Piracy more serious than burglary, fraud, bank robbery
- AT&T willing to spy for NSA, MPAA, and RIAA
- MPAA: We are committed to fair use, interoperability, and DRM

DIGG THIS POST YOUR COMMENT

Reader comments

MrCatbert

I really wish I had studied more biology. This is fascinating stuff.

The NI writers are kicking some serious ass this week - thanks!

November 07, 2006 @ 04:36PM

shannim

Heh. In my high school physics class, if you just had a sphere, it was a horse. Color in a blob in the middle and it turned into a physics cow. I guess that's Texas for ya.

November 07, 2006 @ 06:20PM

kcisobderf

If lost in a crowd, doesn't Dr. Box turn into Dr. Sphere?

November 07, 2006 @ 06:58PM

HodyOne

"The simulations showed that cells would have a large increase in adhesion rate from only a small increase in the height of the knobs. This phenomena is seen in nature as well: both white blood cells and malaria use this "porcupine spine" mechanism. "

I don't see how that follows. Are you saying that white blood cells and malaria have higher "knobs" and also have higher adhesion "rates" because of it?

November 07, 2006 @ 07:14PM

HodyOne

"No longer do advances in computational chemistry|biology|material science|engineering mean a trivial bit of information, but a real step forward in our scientific understanding of a system."

I'm also interested in what you mean by this statement. Are you saying the simulation in this study is a real step forward in our scientific understanding of adhesion? I disagree. It describes a simulation that makes predictions about what are the important parameters for

adhesion, but are those predictions tested in any meaningful way? If not, then how do we know if it's really a useful model?

November 07, 2006 @ 07:16PM

zeotherm

> quote:
> Are you saying that white blood cells and malaria have higher "knobs" and also have higher adhesion "rates" because of it?

HodyOne, yes. It is known that white blood cells have little knobs (not the correct biological term) that stick out about 300nm from the cell surface and they clearly adsorb to a surface presumably at the site of an infection, similarly, when a RBC gets infected with malaria, it is know to develop similar knobs (although much smaller than those observed on a WBC) and stick to advoid being destroyed. I am saying (as far as my biological knowledge will get me) that cells with these features are known to adhere more than those without them.

> quote:
> Are you saying the simulation in this study is a real step forward in our scientific understanding of adhesion?

Yes, I am. Not adhesion in general, but this form of cellular adhesion.

> quote:
> I disagree. It describes a simulation that makes predictions about what are the important parameters for adhesion, but are those predictions tested in any meaningful way? If not, then how do we know if it's really a useful model?

How is identifying the key parameters NOT a step forward in out understanding of a system? See above for experimental corroboration. What the study clearly showed is that it is not the number or size of receptor sites that is important (to a point), but the structure that they have that is the important parameter.

Is your contention that a model/simulation is useless unless it can be tested directly by experimental means? And that it is incapable of being generalized to a larger set of results beyond what it is directly testable for? That, I disagree with.

November 07, 2006 @ 07:52PM

HodyOne

" I am saying (as far as my biological knowledge will get me) that cells with these features are known to adhere more than those without them. "

You haven't presented any evidence for it though. Is there a study that shows a correlation between the ability of a cell to adhere and the height of its "receptor knobs"? If there isn't then I don't know where your statement that "cells with these features are known to adhere more than those without them" comes from.

"How is identifying the key parameters NOT a step forward in out understanding of a system?"

They haven't identified key parameters. They've made predictions about what the key parameters are and until those predictions are tested, they're just predictions.

"Is your contention that a model/simulation is useless unless it can be tested directly by experimental means? "

No, models are useful for making predictions, but until those predictions are tested (i.e. it is understood how well it correlates with the real world), the model is of, uh-uhm, limited usefulness. As an example, what if it was found experimentally that receptor density is critically important for adhesion, beyond that predicted by this model? Or what if the height of "receptor knobs" were experimentally altered and it had no effect on adhesion? In other words, if the results of this modeling study were disproven, would you still find this model useful?

"And that it is incapable of being generalized to a larger set of results beyond what it is directly testable for?"

"Good" models have predictive power, "bad" ones don't.

November 07, 2006 @ 10:32PM

zeotherm

> quote:
> Originally posted by HodyOne:
> " I am saying (as far as my biological knowledge will get me) that cells with these features are known to adhere more than those without them. "
>
> You haven't presented any evidence for it though. Is there a study that shows a correlation between the ability of a cell to adhere and the height of its "receptor knobs"? If there isn't then I don't know where your statement that "cells with these features are

known to adhere more than those without them" comes from.

Malaria infected RBCs stick and have this knobby feature, healthy RBCs are smooth and do not stick. Hence a comparison the authors of the paper were apt to point out. (Malaria refs: E. Nagao, O. Kaneko, and J.A. Dvorak, J. Struct. Biol. **130**, 34 (2000) && L. Bannister and G. Mitchel, Trands Parasitol, **19**, 209 (2003); White blood cell ref: T. A. Springer, Cell **76**, 301 (1994))

> quote:
> "How is identifying the key parameters NOT a step forward in out understanding of a system?"
>
> They haven't identified key parameters. They've made predictions about what the key parameters are and until those predictions are tested, they're just predictions.

They solved a set of equations (Langevin equation) that dictate how cells move through the blood stream and added in their hypothesis of the cause of some sticking and some not. Why is that any more or less valid than doing in in the lab?

They are approximating nature with a set of equations and solving them. Nature will simply solve the Langvien equation in its own way.

> quote:
> "Is your contention that a model/simulation is useless unless it can be tested directly by experimental means? "
>
> No, models are useful for making predictions, but until those predictions are tested (i.e. it is understood how well it correlates with the real world), the model is of, uh-uhm, limited usefulness. As an example, what if it was found experimentally that receptor density is critically important for adhesion, beyond that predicted by this model? Or what if the height of "receptor knobs" were experimentally altered and it had no effect on adhesion? In other words, if the results of this modeling study were disproven, would you still find this model useful?

No, where did I claim this model solved everything perfectly? In fact I went out of my way to say that NO model does that. Limited usefulness is still useful. My car has limited usefullness, it cannot transport me anywhere I want, but it is damn useful at getting me to work and home each day.

If a set of experiments was found to completely invalidate this model, then its usefulness will be reduced to near zero, but as it stands the model quantitatively qualitatively agrees with what is known experimentally (if your interested, see above Refs. detailing malaria and WBCs (which this paper mentions are already at their receptor saturation limit))

As it stands, the researchers sought the simplest model that reproduced some known features about cell adhesion, they then used this *simple* model to try and understand which of the features they added was important, what they found agreed with what is known experimentally, and suggested a *reason* for why that is seen in experiment. <--This is what is important.

> quote:
> "And that it is incapable of being generalized to a larger set of results beyond what it is directly testable for?"
>
> "Good" models have predictive power, "bad" ones don't.

Neither you nor I are the aribter of good and bad models. I suppose in this case the arbiter would be the editor of Phys. Rev. Lett. and those who peer-reviewed the study.

EDIT: I mistyped quantitative agreement(as in exact or near exact match) for qualitative agreement (as in similar trends and behavior). Further corrections in my later post.

November 07, 2006 @ 11:11PM

HodyOne

"Malaria infected RBCs stick and have this knobby feature, healthy RBCs are smooth and do not stick. Hence a comparison the authors of the paper were apt to point out."

Very good of you to provide references. I'll look them up tomorrow when I have online journal access. However, you're basically describing a correlation with n=2 which I hope you will agree is hardly convincing.

"They are approximating nature with a set of equations and solving them. Nature will simply solve the Langvien equation in its own way."

Nature has been approximated with equations incorrectly many times before. As you say, Nature is solving the Langevin equation in its own way, and that may be different than the way it was solved by the researchers (e.g. with different parameters). As an aside, this is representative of the arrogant/naive attitude that is sometimes found in the modeling community (i.e. that nature must follow from the way some equation was applied).

"If a set of experiments was found to completely invalidate this model, then its usefulness will be reduced to near zero, but as it stands the model quantitatively agrees with what is known experimentally"

I'll look up these papers to see exactly how quantitative it is but even still, there's no predictive power here. They knew the answer before they made the model. If the model is

fragile and only applies to a limited set of data, then it's not useful and it's sketchy to draw conclusions from it. The best studies like this actually devise new experiments based on the predictions from their model to test it.

"Neither you nor I are the aribter of good and bad models. I suppose in this case the arbiter would be the editor of Phys. Rev. Lett. and those who peer-reviewed the study."

I hope you're not implying that bad models haven't been published in Phys. Rev. Lett., Science, Nature, Cell or any other journal.

November 07, 2006 @ 11:55PM

zeotherm

HodyOne, before I go to bed, I first need to point out a typo in a claim I made (I'll go back and make note of the correction in my previous reply). I should have said that the model is in **qualitative** agreement with experiment, not quantitaive. That was a mis-fired neuron on my part. The authors of the original paper do not claim this to be qualitative.

> quote:
> If the model is fragile and only applies to a limited set of data, then it's not useful and it's sketchy to draw conclusions from it. The best studies like this actually devise new experiments based on the predictions from their model to test it.

The authors discuss both at the begining and endof the letter how the results discovered here can be applied to bio-nanotech applications such as cell sorting and how it can be extended to understanding of how some bacteria behave. Perhaps I am not sure what you are looking for from a research article. This paper, used simulation methodology to give new insight into a problem. This is one of the main purposes of science, to give insight into a problem of the natural world, and I fail to see how this paper does not accomplish that. Would we be having the same discussion had this been an experimental paper?

As for the Langvien equation, it is well accepted that it is very well capable of describing the brownian dynamics of a particles in a hydrodynamic flow field. By experimentalists and theorists alike.

> quote:
> I hope you're not implying that bad models haven't been published in Phys. Rev. Lett., Science, Nature, Cell or any other journal.

Nowhere did I say that, nor is it relevant to the discussion at hand. And no, nowhere am I implying that a bad model (or bad experiment) hasn't gotten through into a top teir journal. I am implying that we are not the judges of a model's (or experimental data set's) ultimate utility, only time will tell us

that. However a solid understanding of the basics of computational science (or the field of any newly reported data) will help you in understanding if a model (or data) is worth a second look.

November 08, 2006 @ 12:15AM

robotic_tourist

This is Ars and I can't believe that no one picked up that rather than a porcupine, the cell is actually being modelled as an Amiga, possibly as a demo for Amiga hardware and/or the latest Amiga OS

November 08, 2006 @ 07:43AM

HodyOne

"This paper, used simulation methodology to give new insight into a problem. This is one of the main purposes of science, to give insight into a problem of the natural world, and I fail to see how this paper does not accomplish that."

That's the argument. I'm saying that this is a model that makes predictions that need to be tested more fully for the model is interpreted as an accurate description of the system being modeled.

"As for the Langvien equation, it is well accepted that it is very well capable of describing the brownian dynamics of a particles in a hydrodynamic flow field. By experimentalists and theorists alike."

Like I said before, just because the Langevin equation is used doesn't mean the model is correct.

"I am implying that we are not the judges of a model's (or experimental data set's) ultimate utility, only time will tell us that."

But we are both judging this model. You're judging it as a correct model of reality and I'm judging that it hasn't been tested anywhere near adequately to make that conclusion.

November 08, 2006 @ 09:53AM

kingdom2

in architecture, still, even after the pc revolution, models are
physically built. designers who do are called "cardboard architects" and generally believe in the "zen" that (they are)
designing "what is not there" and are the bane of engineers
sometimes:weird how this discussion echos

November 08, 2006 @ 10:36AM

DIGG THIS POST YOUR COMMENT