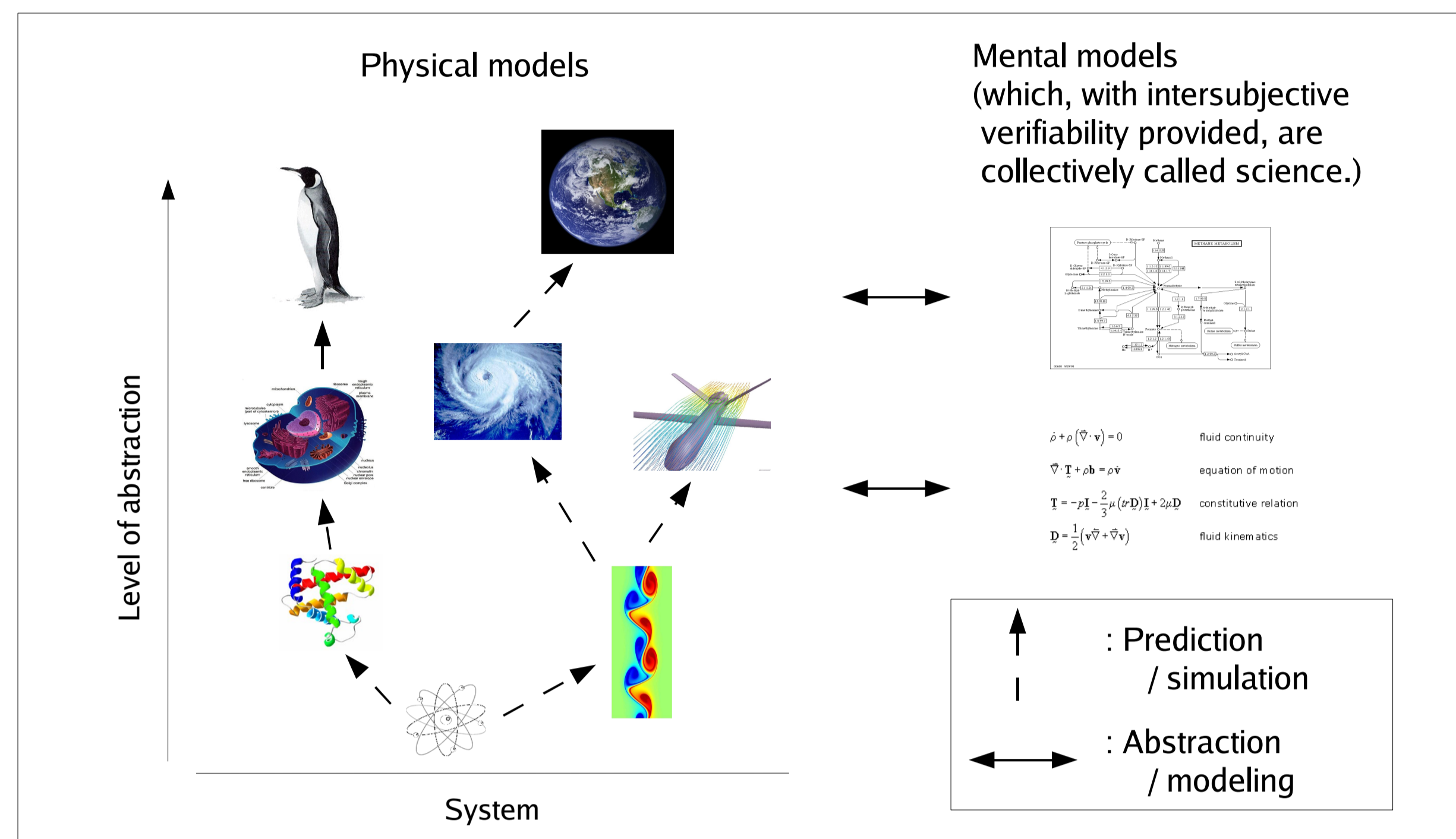


Introduction

What's understanding, and how can we test if we understand the way the world surrounds us works?

- Can that new understanding find isomorphism in other systems? (abstractive power test)
- Can that new understanding show how behavior of the system at a neighboring level emerges? (predictive power test)



Two things numerical simulation can do

- Interpolation
 - Given a set of physical laws (in a broad sense) and an experimentally determined set of input parameters, a computer program can enable us to study the system based on quantities beyond our accessibility due to technological or sometimes more fundamental limitations.
- Extrapolation
 - It can also show us how the system would behave in a condition different from the one under which the input parameters were taken.

Problem

What we can do (or making good progress) in year 2006:

- Characterizing / predicting / seeing molecular interactions between gene products.
- Measuring abundance/concentration of nearly any molecular species in a cell or a population of cells.
- Seeing localization of proteins and some other molecules.
- Efficiently instantiate trajectories from a chemical master equation (CME), reaction rate differential equations (RRDE) or diffusion-reaction partial differential equations (DRPDE).

What we cannot do yet:

- Direct measurement of *in vivo* reaction rates or predicting such quantities from a DNA sequence or molecular structures.
- Knowing the role of intracellular space in cellular biochemistry, and producing trajectories properly taking into account of such effects.

Two vital breakthroughs we will need to see if we want to bring the true abstractive/predictive powers of modeling & simulation into molecular systems biology:

1. Computational and chemico-physical aids in determination of biochemical reaction rates.
2. Formal and efficient numerical treatment for simulation of intracellular media.

Reaction rates

Ok, the last ten years of simulation in molecular biology has undeniably been (re)discovery of our inability to obtain reaction rate coefficients easily.

Why is it so difficult?

- 1) Because all what we can indirectly see with concentration timeseries is net change (sum of multiple reactions, degradation, bleaching etc.), not a particular reaction rate.
- 2) Plus, because there are no such physical quantities like reaction rate coefficients, but there are only physico-chemical molecular interactions subsequent to diffusive encounters between reactants.

- $1 / \text{Net reaction rate} = \text{Reaction time} = \text{time to encounter by diffusion} + \text{time to react upon contact}$

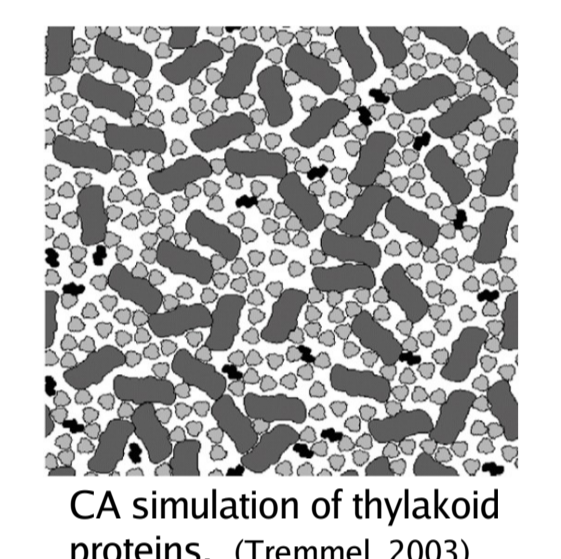
$$\frac{1}{k_{net}} = \frac{1}{4\pi\sigma D} + \frac{1}{k_a}$$

- Smoluchowski rate coefficient
 $k(t) = 4\pi\sigma^2 D \frac{\partial C}{\partial r} = 4\pi\sigma D \left(1 + \frac{\sigma}{(\pi Dt)^{1/2}}\right)$
 $k(\infty) = 4\pi\sigma D$

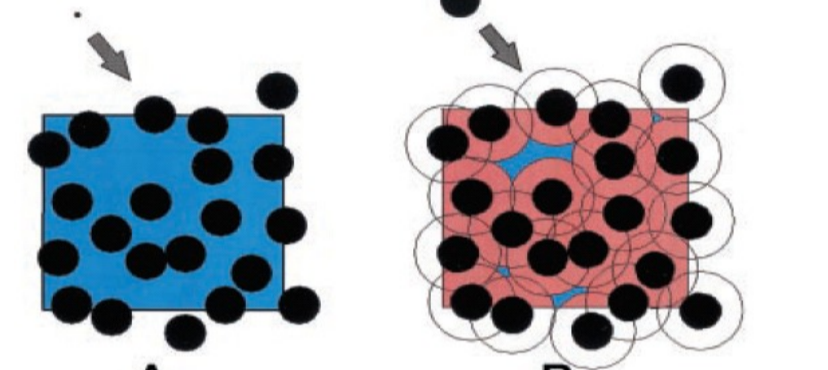
Intracellular Space

Space can modify biochemistry

- **Diffusion** is ~10x – 20x slower in cytosolic media than in saline solution. Diffusion limited reactions can amplify noise.
- **Localization** can modify system characteristics of the pathway when coupled with diffusion.
- Intracellular space is **crowded**; 50 – 400 mg/ml. ~20-40% of cytosolic volume is 'excluded' by macromolecules. Soft matter physics predicts easily more than 100x increase in activity coefficients, which affect equilibria and reaction rates. It alters the manner of diffusion (e.g. anomalous sub-diffusion).



CA simulation of thylakoid proteins. (Tremmel, 2003)

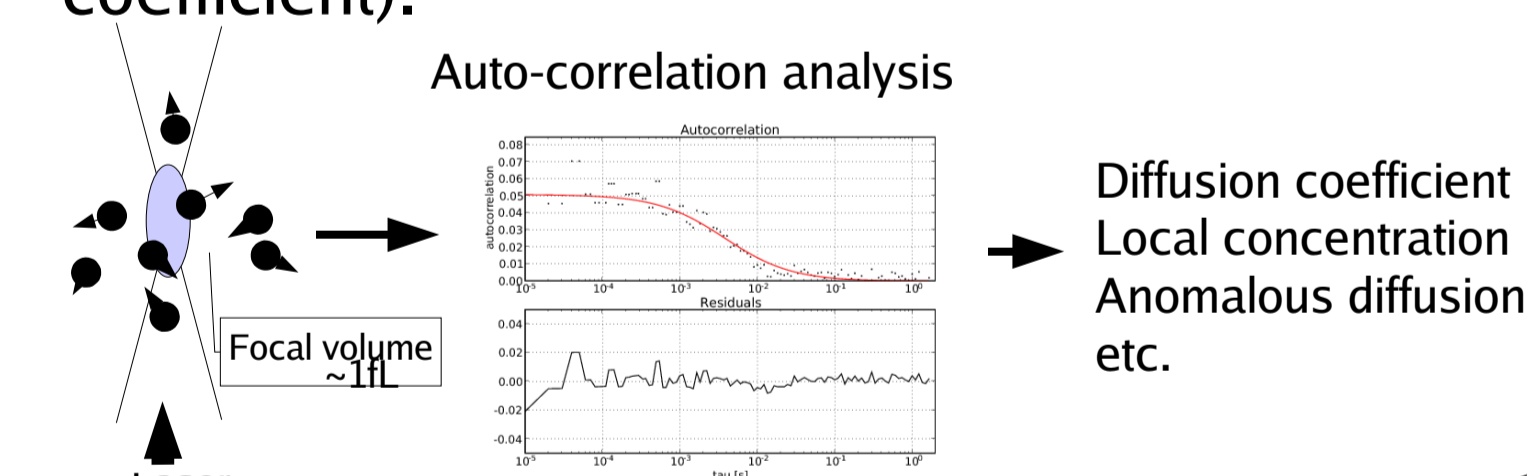


Blue: available, Red: excluded (Minton, 2001)

One Possible Approach

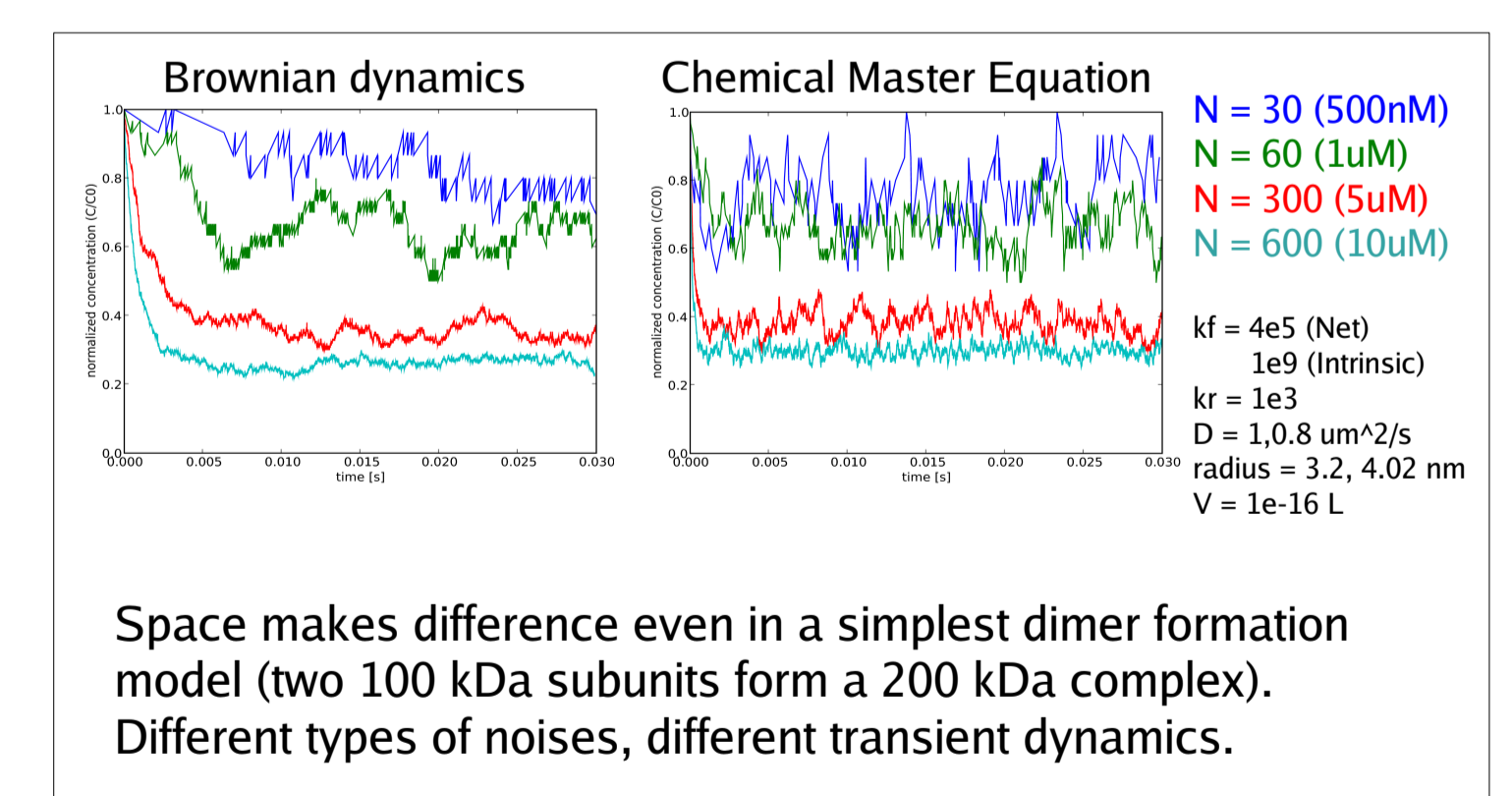
$$\frac{1}{k_{net}} = \frac{1}{4\pi\sigma D} + \frac{1}{k_a}$$

This part is physically much better grounded, thanks to Einstein and Smoluchowski. Fluorescent correlation spectroscopy, for example, can be used to obtain D (diffusion coefficient).



Intrinsic reaction rate k_a is determined by activation energy. We don't have a high-throughput means to calculate activation energy for enzymatic reactions yet. However, energy barriers involved in complex formations are supposed to be low, and be relatively easy to estimate with computation or experiments. --> Signaling pathways

Brownian Dynamics (BD) simulation of signaling pathways can not only better represent intracellular media, but also be a solution to the biggest bottleneck in modeling, obtaining reaction rate coefficients, in biochemical modeling and simulation work flow. Emerging accelerated BD techniques such as GFRD could drive realistic biochemical models in whole cell space efficiently.



Space makes difference even in a simplest dimer formation model (two 100 kDa subunits form a 200 kDa complex). Different types of noises, different transient dynamics.

Summary

- Highly desired breakthroughs for molecular biological simulation to be more useful:
 - (1) Reaction rate coefficients.
 - (2) Intracellular space.
- Particle simulation (Brownian Dynamics) can make modeling of signaling pathways easier with a concomitant and possibly acceptable loss of computational efficiency.

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