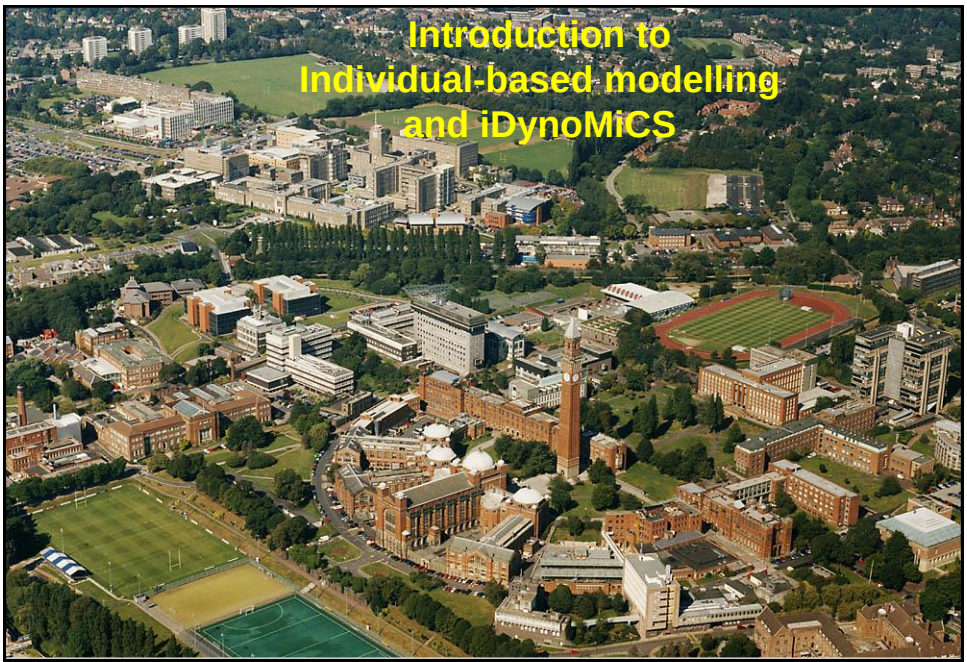


Introduction to Individual-based modelling and iDynoMiCS

Jan-Ulrich Kreft, Centre for Systems Biology, School of Biosciences, University of Birmingham, j.kreft@bham.ac.uk

Science is what we understand well enough to explain to a computer. Art is everything else we do.

Donald Knuth

Individual-based Modelling

What is Individual-based Modelling?

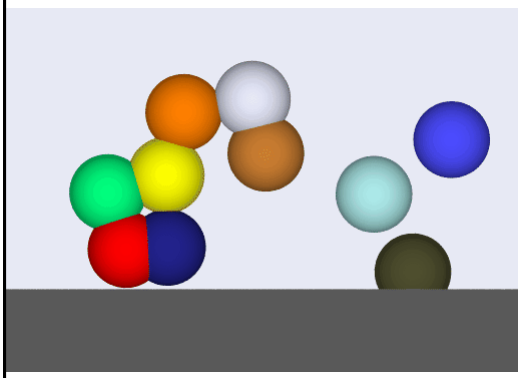
- In an individual-based model, we
  - describe the activity/behaviour of each individual organism
    - allowing for differences between individuals of the same species
    - usually stochastic (not deterministic)
  - describe the properties and processes of the environment
    - usually spatially explicit
  - nothing else!
  - because everything else is emergent
    - feedbacks
    - competition
    - fitness
    - spatial structure
    - age, size, ... structure

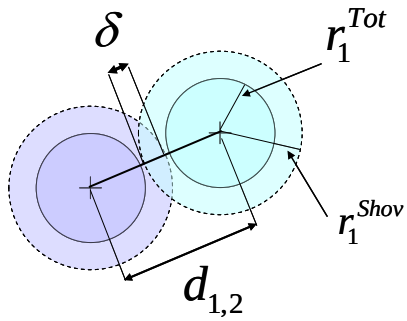
Emergence and predicting interactions

Alexander Fleming's Petri dish with *Penicillium* and *Staphylococcus* 1928

- Studying all possible interactions between species in a community leads to combinatorial explosion of the number of experiments required
- $2^N - 1$
- Kreft et al. (2013) Mighty small: Observing and modeling individual microbes becomes big science. PNAS 110: 18027-18028

More examples of emergence: shoving rule leads to expansion of growing colony



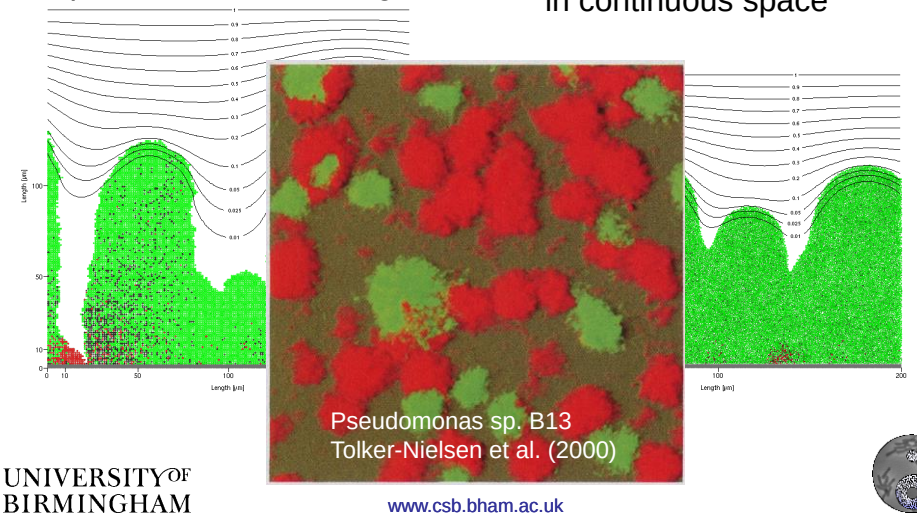


$$\delta = d_{1,2} - k_{Shov}\left(r_1^{Tot} + r_2^{Tot}\right)$$

Biomass spreading in *multispecies* biofilm models

Cellular Automaton: displacement rules on a grid

IbM: shoving of spheres in continuous space



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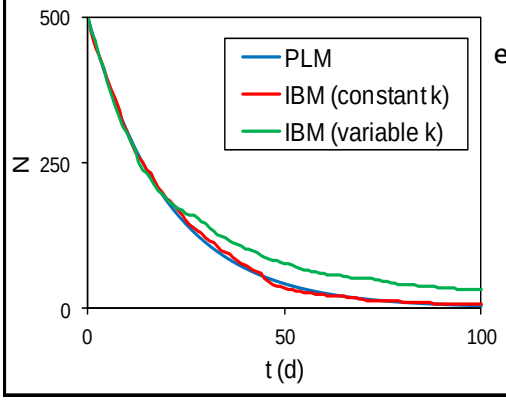
Population-level versus Individual-level

- Exponential death of a population

$$\frac{dN}{dt} = -k\,N \qquad N = N_0\,e^{-k\,t}$$



- Probability of death of individuals

```
for each time step
   for each individual
       die with probability p
       end if
   end for
end for
```

When to use IbM?

- Use IbMs only if these three are considered crucial:
  - (i) variability among individuals
  - (ii) local interactions
  - (iii) adaptive behavior

When to use IbM?

- For example if
  - feedbacks between individuals' activities and environmental resources cannot be captured by average properties of individuals (nonlinearity)
  - the variation between replicate simulations of a small number of individuals in the system is of interest
  - events are considered, i.e. rare and sudden occurrences such as metabolic switches, differentiation into persisters or dormant spores, phase variation of the cell surface, infection by a plasmid or phage, entering/leaving a host cell or migrating to a new patch
  - rare variants in a population are important for division of labor or as an insurance mechanism for survival of stresses
  - rare species in a community with only few individuals are important (keystone species)
  - mutations are to be modeled in an evolutionary IbM

Do not use IbMs

- when none of the three defining features of IBMs is considered essential
- when there is insufficient knowledge to describe and parameterize individual behavior, unless a purely theoretical model is intended
- when you are interested in processes on a much larger scale or higher level than community dynamics

Don't

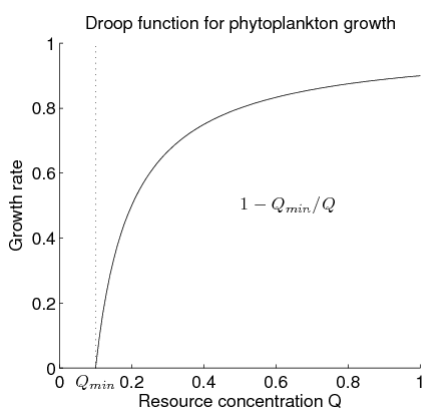
- impose that behavior of individuals one wishes to study as emergent
  - Imposing behavior means to prescribe it via rules or equations so that one obtains exactly the behavior that was specified, leaving no room for surprises
- use global environmental or population states to decide the cell's activities; cells do not have global knowledge
- use parameters that are impossible to measure

Do

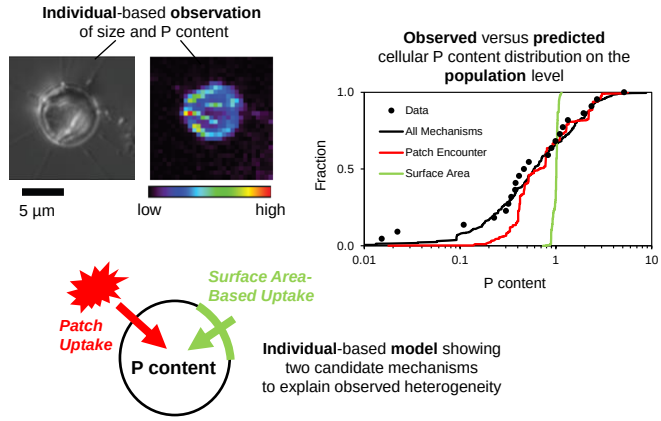
- describe individual behavior without thinking about any population level consequences
- use mechanistic rather than phenomenological descriptions of individual behavior if possible
- use data measured at the level of individual cells or where that is not possible consider the relationship between individual and population level parameters (you can use the IbM for this) and how central this aspect is to the question you want to address

Non-linearity and the fallacy of averaging

- If the response of an organism to some variable (e.g. a drug, nutrient, stress) is non-linear, then the average of the responses to the fluctuating dose over time is different from the response to the average dose
- This is known as Jensen's inequality (Jensen 1906)
- Example: non-linear function describing growth rate of phytoplankton as a function of nutrient concentration (Droop model)



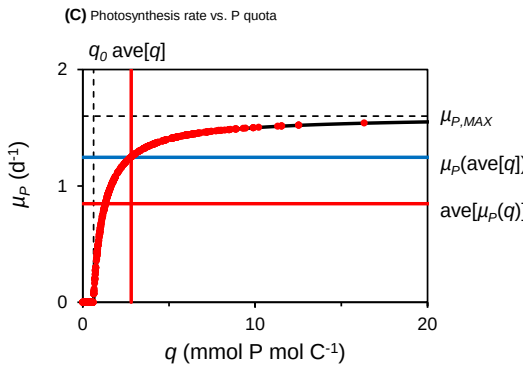
Non-linearity and the fallacy of averaging



Observing and modeling individual heterogeneity in intracellular P content in the freshwater diatom *Cyclotella meneghiniana*.

Kreft et al. (2013) Mighty small: Observing and modeling individual microbes becomes big science. PNAS 110: 18027-18028

Non-linearity and the fallacy of averaging



Droop kinetics
(1968)

$$\mu = \mu_{\max}\left(1 - \frac{Q_{\min}}{Q}\right)$$

Variation of P content affects population growth rate since growth rate is a nonlinear function of the internal P content. In this case, population-level growth rate is only 68% of the growth rate a population of cells with average P content would have.

Bucci, V., Nunez-Milland, D., Twining, B. & Hellweger, F. (2012) Microscale patchiness leads to large and important intraspecific internal nutrient heterogeneity in phytoplankton. *Aquat Ecol* **46**: 101-118

Simple or complex?

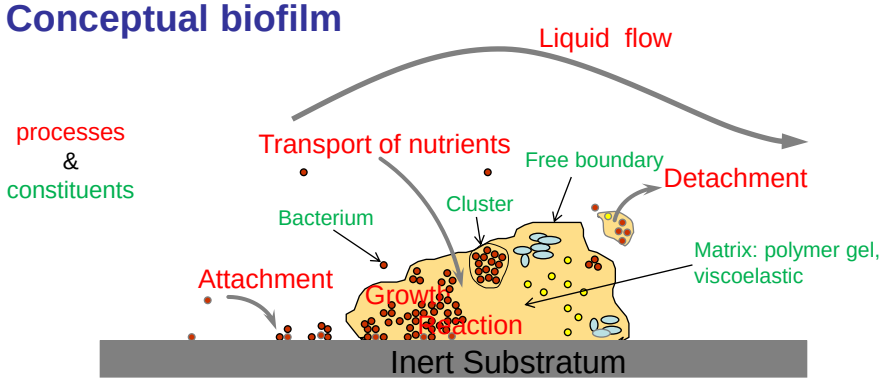
- Conceptually simple
  - describe what individual organisms do
  - describe the environment in which they live
- Computationally complex
  - complex software, difficult to test and communicate
  - complex output of simulations, difficult to analyse and visualise

IbMs make better use of more types of data

	individual-based model		population-based model	
	direct input	compare to model output	direct input	compare to model output
individual-level data	+	+	(+)	–
population-level data	(+)	+	+	+

The importance of spatial structure

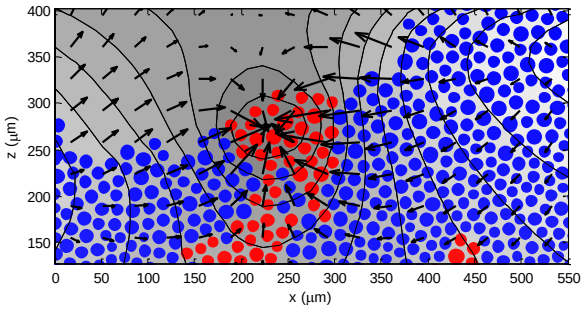
Conceptual biofilm



'Definition' of biofilms: Microbes attaching to and growing on an interface create a structured microenvironment to which they adapt in turn.

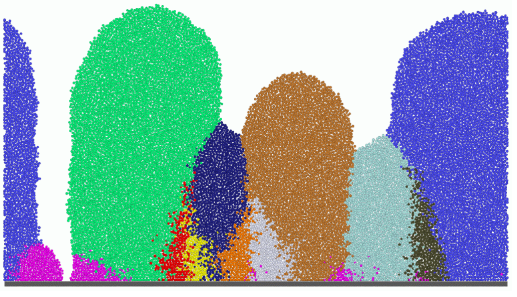
Biofilms: Life in a City

The importance of being spatial



Environmental gradients

Population structure
(population viscosity):
clonal or mixed?



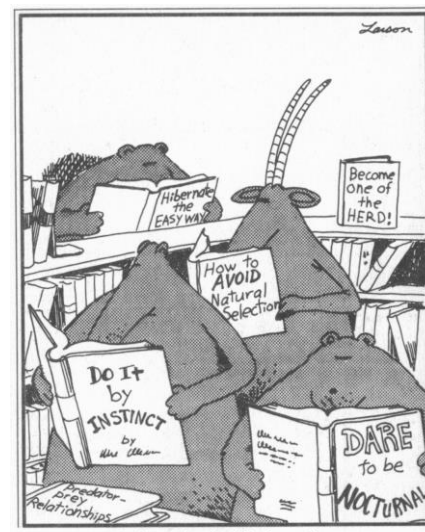
The importance of stochasticity and individuality

Microbial cells are individuals

- Diversity within a population
  - Genetic diversity: mutations happen
  - Phase variation
  - Phenotypic diversity
    - Cell cycle
    - Age
    - Noise in gene regulation or signalling
    - 'Micro'-environment
      - Gradients of nutrients
      - Gradients of signals
      - Some cells upregulated, some downregulated
    - History of the above
- Insurance hypothesis: division of risks (Yachi & Loreau '99)
- Division of labour

Example: Persisters

- Persister cells survive antibiotic treatment because they are 'dormant'
- This is not resistance, there is no mutation
- Resistance is heritable
- Persisters are isogenic, but phenotypically different
- They don't grow, so are outcompeted by normal cells in the absence of stress
- How is natural selection avoided?



In the animal self-help section

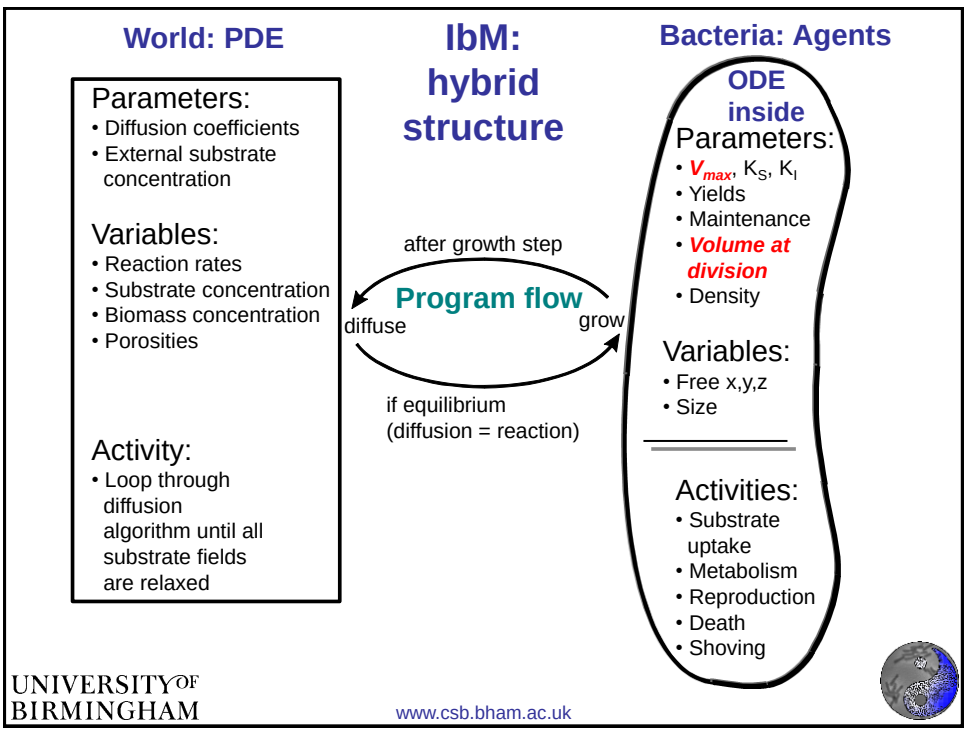
iDynoMiCS:
a generic platform for individual-based modelling of microbes

Potential problems of isolated model development

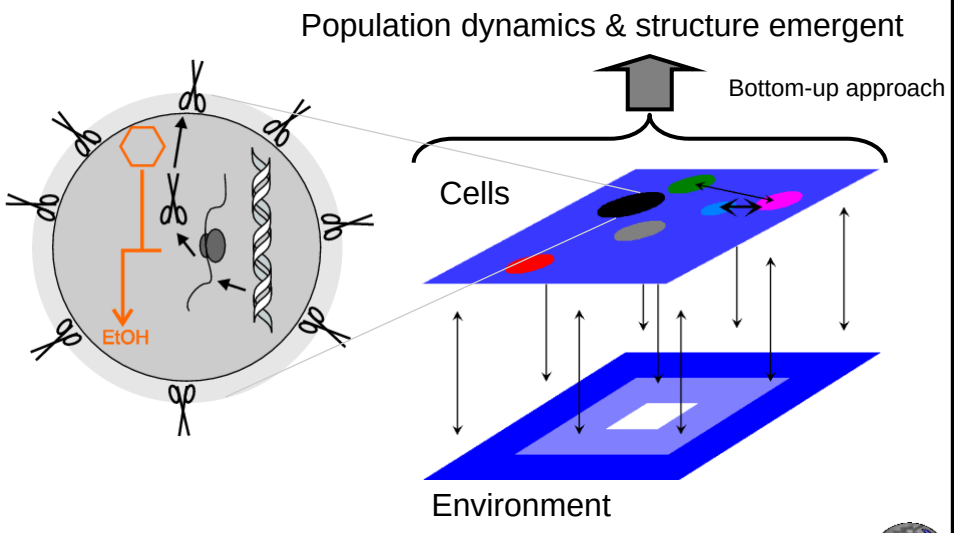
- No testing of structural robustness of model due to
  - Single environment
  - Incomplete physics
  - Lacking biological processes
- Requirement of programming skills
  - Logical/analytical thinking always required
- Difficulties of
  - Comparability of models (do minor differences matter?)
  - Communication of model
  - Reviewing of model
  - Validation of model

Solution: generic platform

- Generic platforms enable
  - Testing structural robustness not only parameter sensitivity
  - Synergies
    - Clearer comparison of work of different groups
    - Common basis for communication
    - Shared development effort
    - Shared know how
    - Testing code not only by coder
  - Autocatalytic growth, the better the platform, the more people will use it, the more people use and test and develop, the better the platform
    - Need sufficient capability and critical mass of users to get the positive feedback going
  - Modelling without lots of difficult programming
    - But software doesn't make decisions for you



Individual-based Modelling (IbM) of interactions



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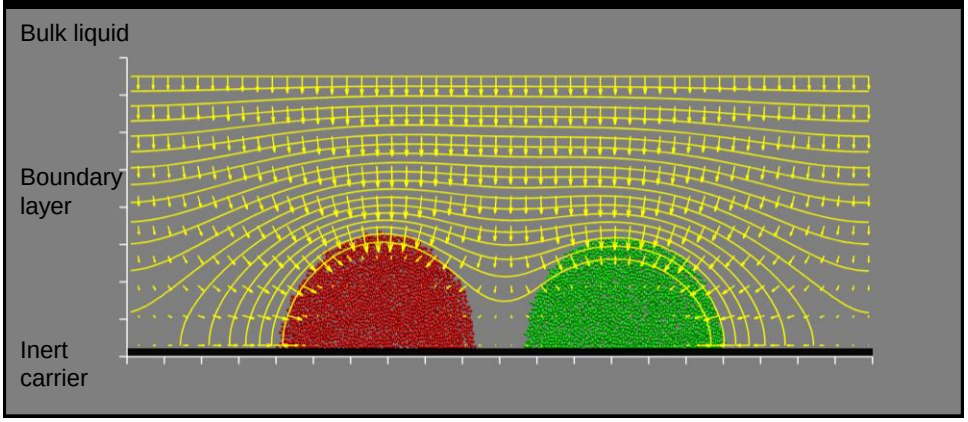
Agents and solute concentration fields



Problems of model and software development

- Bugs
- Validation
- Lack of key processes
- Comparability
- Communication

iDynoMiCS is going crowd

- Code on github for everyone to see, use, change, raise issues
  - including wiki for tutorials & FAQ & help
- Open consultation for development plans
- Crowd sourcing bug hunting
  - £30 Amazon voucher for every bug found
  - Certificate of programming proficiency for other contributions
- Mailing lists
  - idynomics@lists.bham.ac.uk
  - idynomics-announce@lists.bham.ac.uk

iDynoMiCS
iDynoMiCS - individual-based Dynamics of Microbial Communities Simulator

www.idynomics.org

eGUT – electronic gut

NC 3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research

www.egut.org.uk

Further reading

- Grimm V & Railsback SF (2005). Individual-Based Modeling and Ecology. Princeton University Press, Princeton
- Railsback SF & Grimm V (2012). Agent-Based and Individual-Based Modeling: A Practical Introduction. Princeton University Press, Princeton, NJ
- Hellweger FL & Bucci V (2009). A bunch of tiny individuals-Individual-based modeling for microbes. Ecological Modelling 220: 8-22
- Kreft JU (2009). Mathematical modeling of microbial ecology: spatial dynamics of interactions in biofilms and guts. In: Jaykus LA, Wang HH & Schlesinger LS (eds) Foodborne Microbes: Shaping the Host Ecosystem. ASM Press, Washington, DC, pp 347-377

Thanks to the team

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  - Robert Clegg, Kieran Alden, Sónia Martins, Susanne Schmidt, Chinmay Kanchi at University of Birmingham

iDynoMiCS

iDynoMiCS - individual-based Dynamics of Microbial Communities Simulator

www.idynomics.org