

An Overview of Individual-based Simulations in Population Genetics and Cancer

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Lab seminar

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GOALS

- Understand what is a simulation
- Learn how to build an Agent Based Model
- Explore how Agent Based Models had been used in cancer research

What is a (computer) simulation?

- An attempt to mimic a real-world empirical system
- The creation *in silico* of a possible world using computer programs to represent the processes under consideration

Simulations as experimental systems

- Models could be as complex as the real systems they mimic
- A huge advantage: **models are strongly manipulable**
- Simulation models are properly explored using the same experimental and statistical techniques that are used to explore real-world systems

genetic data simulation algorithms

- Backward-time (Coalescent)
- **Forward-time**
- Resampling

Individual/Agent Based Models (IBMs/ABMs)

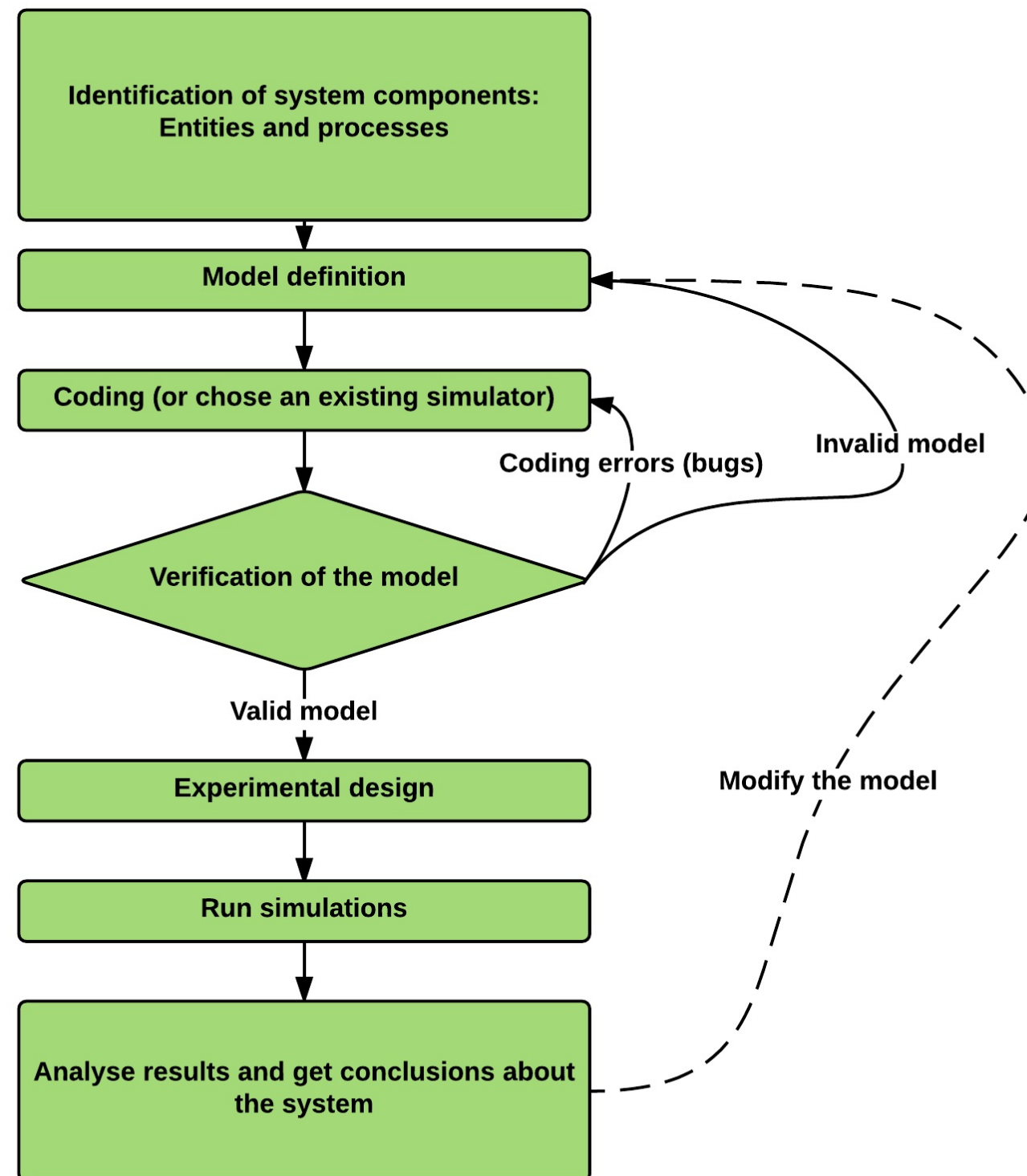
- Simulation models describing individual organisms (agents)
- How system level properties emerge from the adaptive behaviour of individuals and how the system affects individuals
- Aspects usually ignored in analytical models: individuals variability, local interactions, life cycles, ...
- More complex in structure than analytical models and then more difficult to analyze, understand and communicate

Structure of an ABM

1. A set of agents, their attributes and behaviours.
2. A set of agent relationships and methods of interaction:
An underlying topology of connectedness defines how and with whom agents interact.
3. The agents' environment: Agents interact with their environment in addition to other agents.

Agents repeatedly and discretely execute their behaviours and interactions.

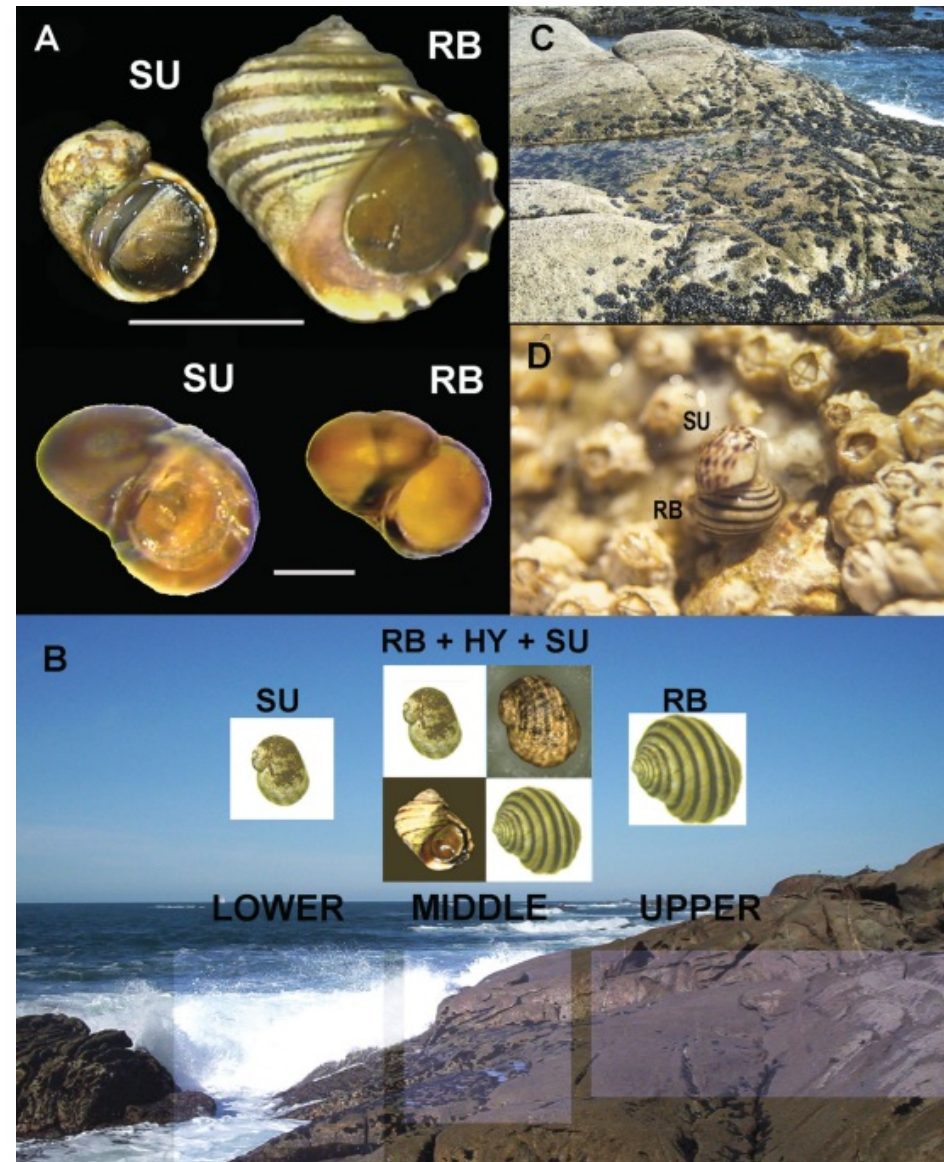
Building a simulation study



Some Population Genetics simulators

a	b	c	d	e	f
Life history	Demography	Selection	Migration	Recombination	Suitable simulators
Complex	Complex	Complex	Complex	Yes, var	QuantiNemo ^{xy}
Complex	Complex	Complex	Basic	Yes	ForSim
Complex	Complex	Complex	Basic	Yes, var	SimuPop ^{xy}
Complex	Complex	Complex	None	Yes, var	QMSim
Complex	Complex	Basic	Complex	No	Vortex
Complex	Complex	Basic	Basic	Yes, var	SFScode [*]
Complex	Complex	None	Complex	Yes	Easypop
Complex	Complex	None	Complex	No	RmetaSim, KernelPop, Spip
Complex	Basic	Complex	Complex	No	Pedagog
Complex	Basic	Complex	Basic	Yes, var	Mendels Acc
Complex	Basic	Complex	Basic	Yes	Nemo [*]
Complex	Basic	None	None	No	BottleSim
Complex	Constant	None	None	No	cdpop
Basic	Complex	None	Complex	No	AquaSplatche [*] , Splatche [*] , IBDsim
Basic	Complex	None	Basic	Yes, var	SerNetEvolve, fastsimcoal ^o , SimCoal2, Genome, mshot, cosi
Basic	Complex	None	Basic	Yes	Coasim, ms
Basic	Complex	None	Basic	No	BayeSSC [*]
Basic	Complex	Basic	Basic	Yes, var	mlcoalsim, mbs
Basic	Complex	Complex	Basic	Yes, var	msms
Basic	Basic	Basic	Basic	Yes, var	GenomePop
Basic	Basic	None	Basic	Yes, var	MaCS
Basic	Basic	None	None	Yes, var	SNPsim
Basic	Basic	None	None	Yes	FastCoal
Basic	Basic	None	None	No	CoalFace
Basic	Constant	Complex	Basic	Yes	FPG
Basic	Constant	Complex	None	Yes, var	GenomeSimla
Basic	Constant	Basic	Basic	Yes, var	FreGene
Basic	Constant	Basic	None	Yes, var	SelSim
Basic	Constant	Basic	None	Yes	ForwSim, Gene Artisan

An old example (from my Thesis)



Problema: ¿Qué fuerzas evolutivas modelan el polimorfismo observado en *Littorina saxatilis*?

Entidades:

- Poblaciones
- Individuos
- Carácter (Ecotipo)
- Cromosomas
- Loci

Procesos:

- Apareamiento
- Supervivencia
- Migración
- Asignación de fenotipo

Modelos con diversos factores:

- Aislamiento reproductivo
- Selección
- Flujo génico
- Número y tipo de loci
- Plasticidad fenotípica
- Definición de ecotipos

Programación mediante lenguaje C:

- Entidades - variables y matrices
- Procesos - funciones
- Factores - parámetros

Ejecución de varios modelos posibles

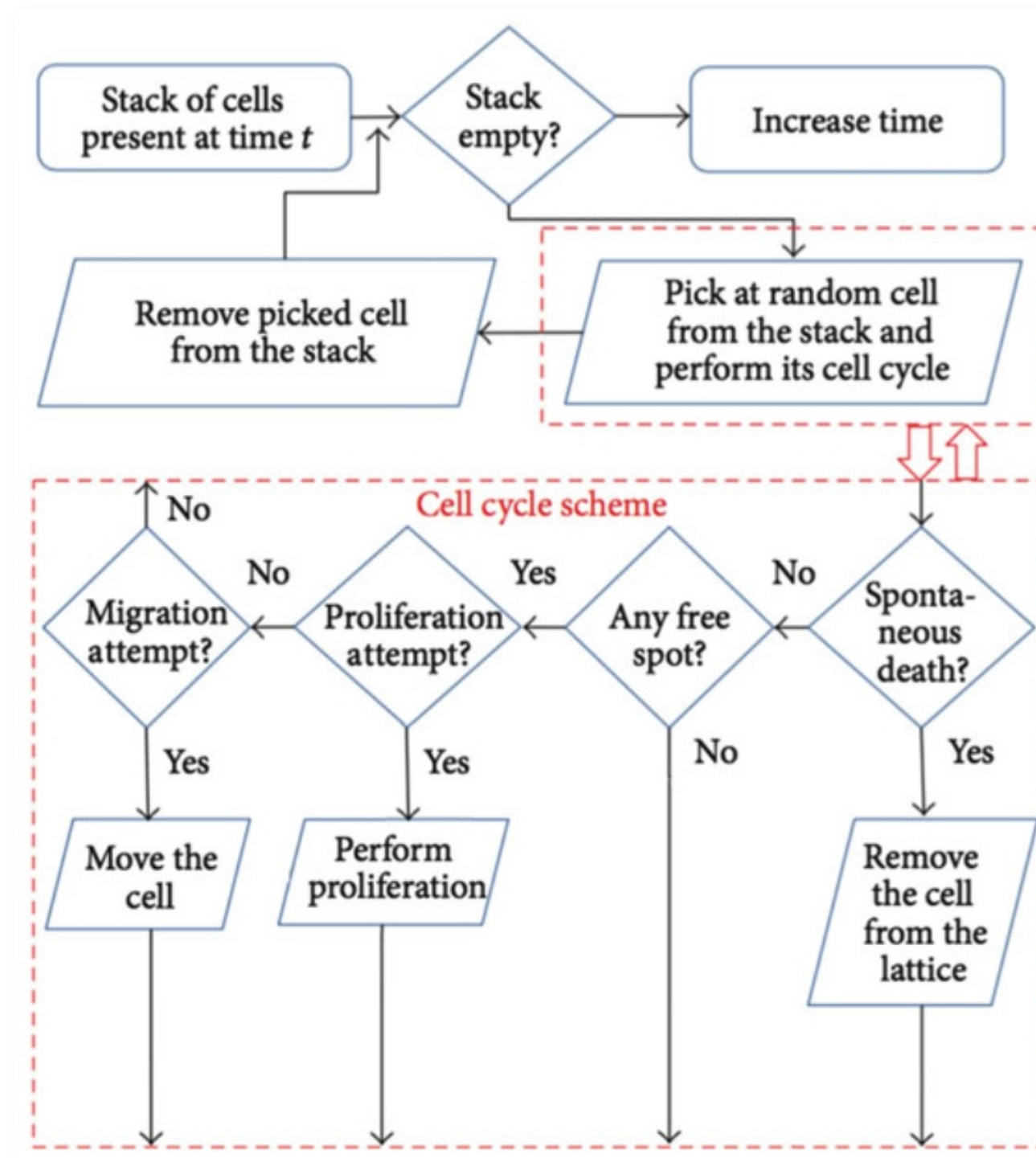
Análisis de resultados:

- Comparar variables de simulaciones con valores medidos experimentalmente (índice de ajuste).
- *El modelo con menor índice de distancia explicará mejor el sistema.*

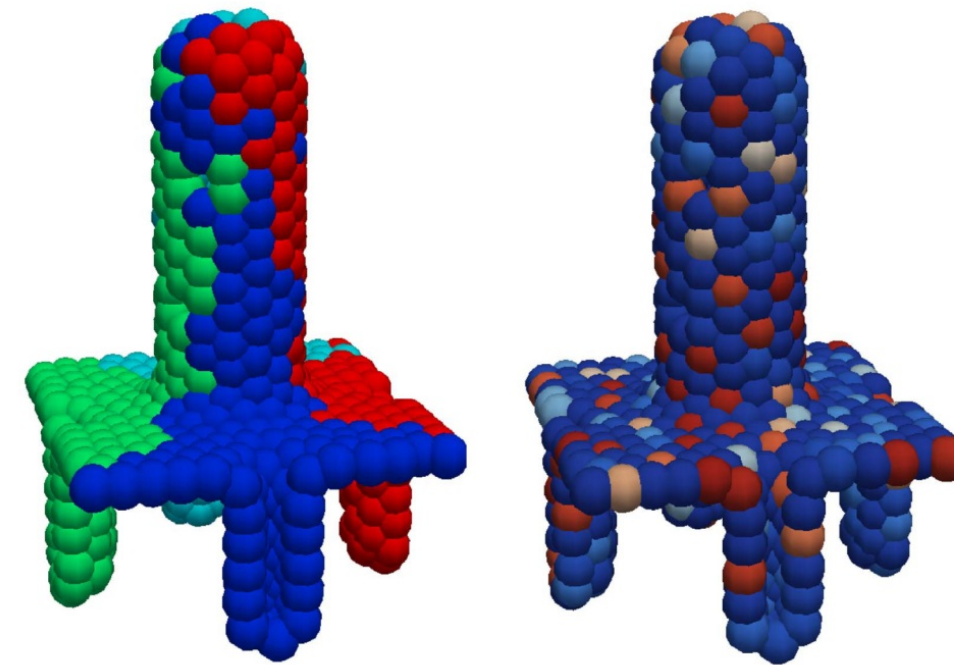
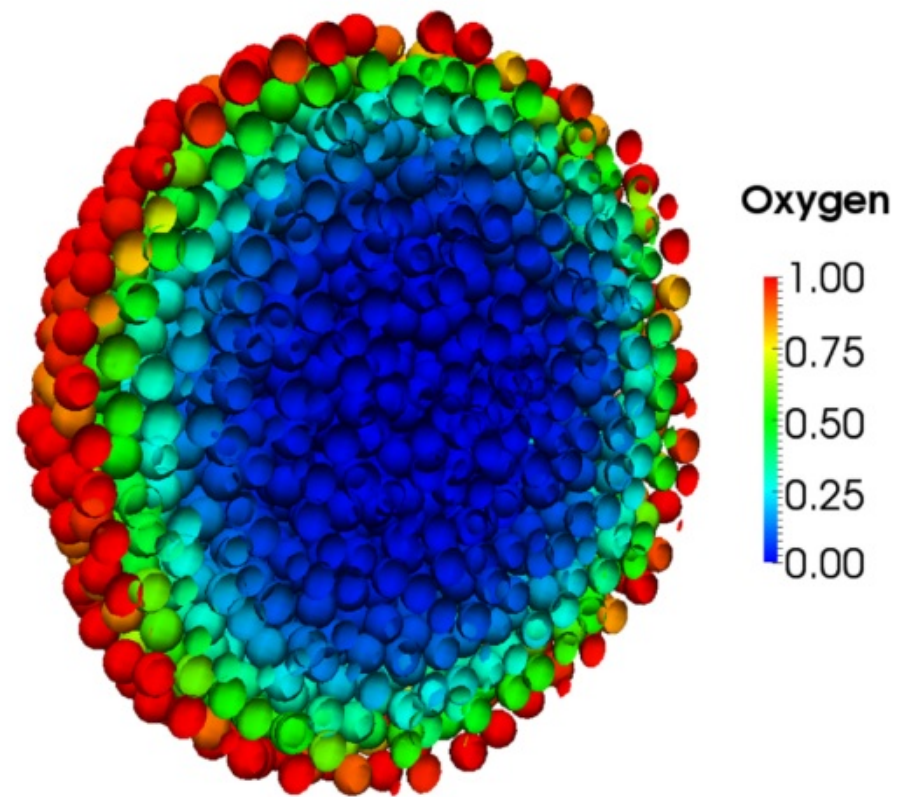
ABMs in cancer research

- Tumor growth
- Phenotypes
- Dynamics of mutation accumulation
- Mostly deterministic laws (PDE)

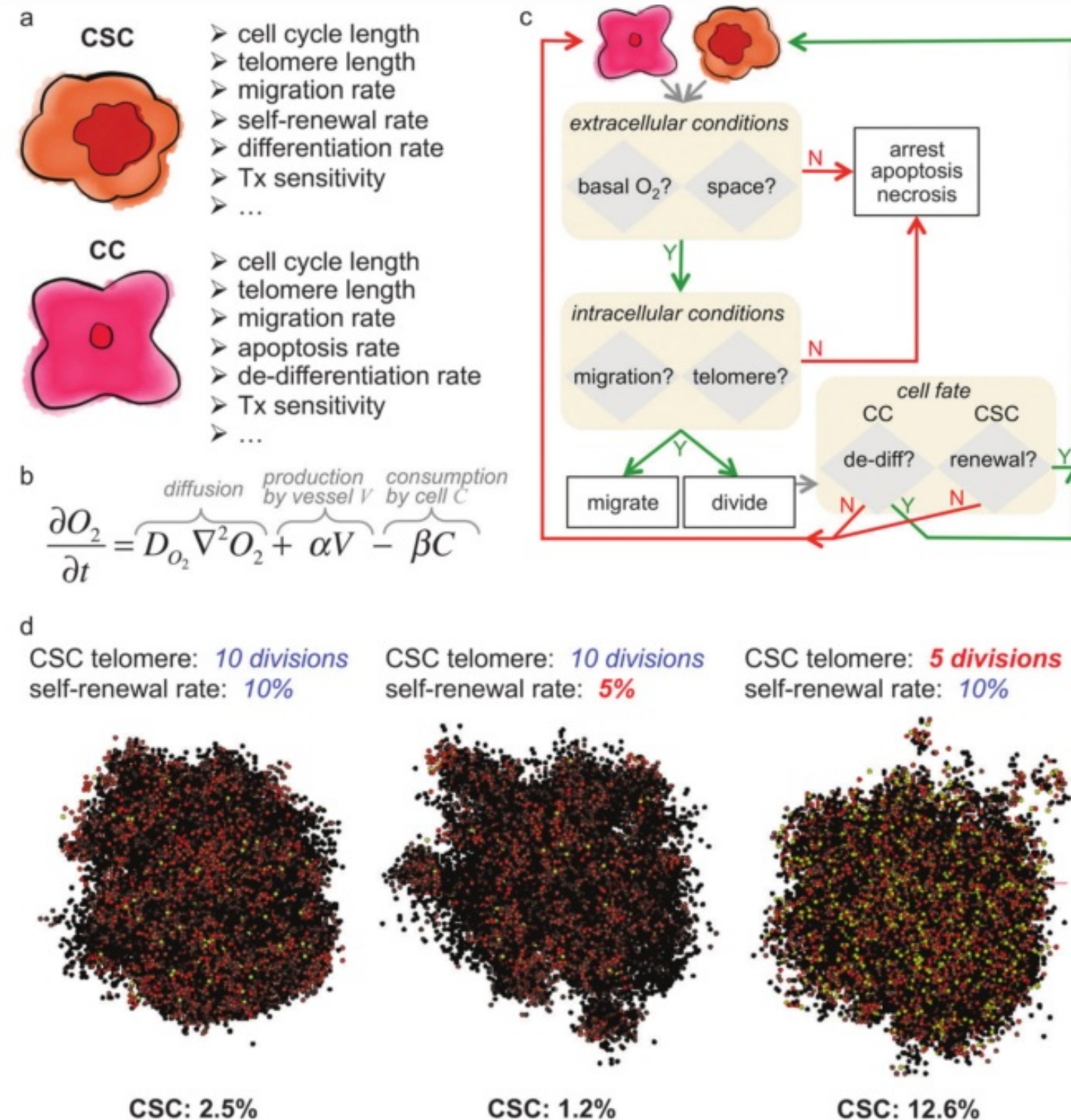
examples ABM in cancer



examples ABM in cancer



Enderling 2014 (CSC)



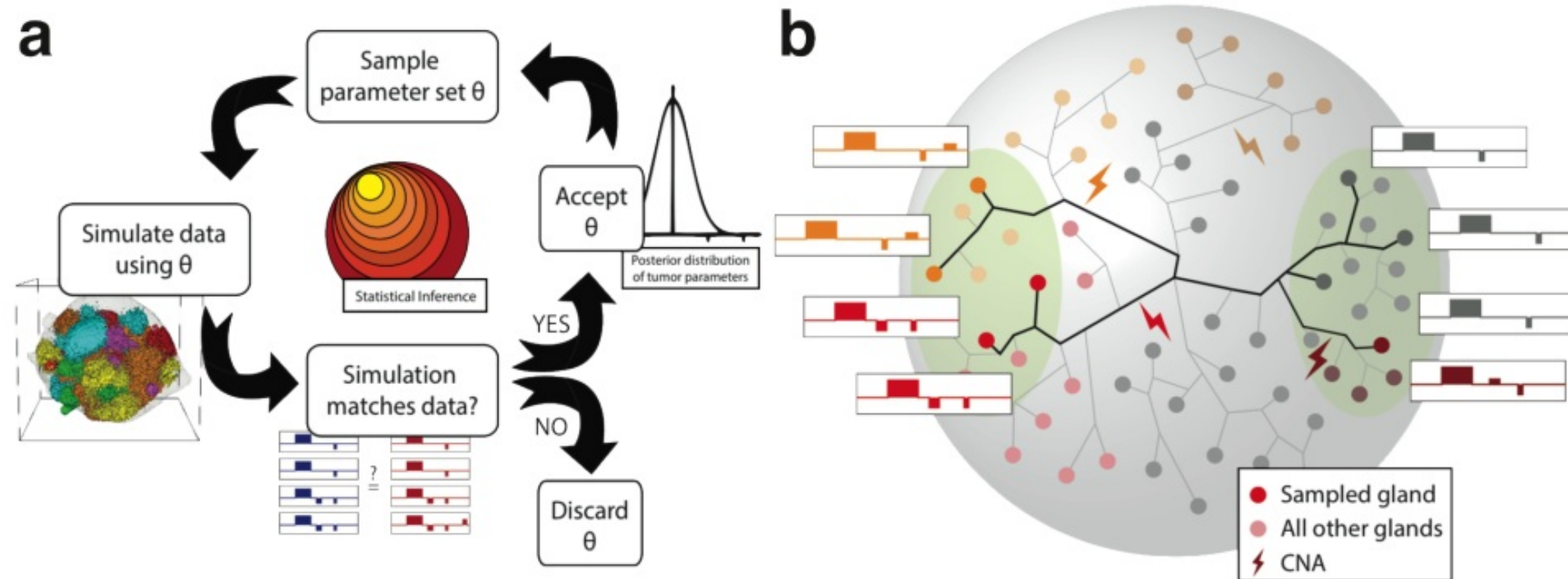
Sottoriva 2015 (Big Bang in CRC)

- Agents: Glands (8M -> 80 billion cells)
- Growth by fission (variable rates), occurrence of CNAs and mutations
- All cells in a gland same fitness (survival and growth)
- Parameters: mutation rate and fitness change
- Not modeled: cellular migration, apoptosis within a gland, the contribution of the surrounding normal tissue or angiogenic factors.

Sottoriva 2015 (Big Bang in CRC)

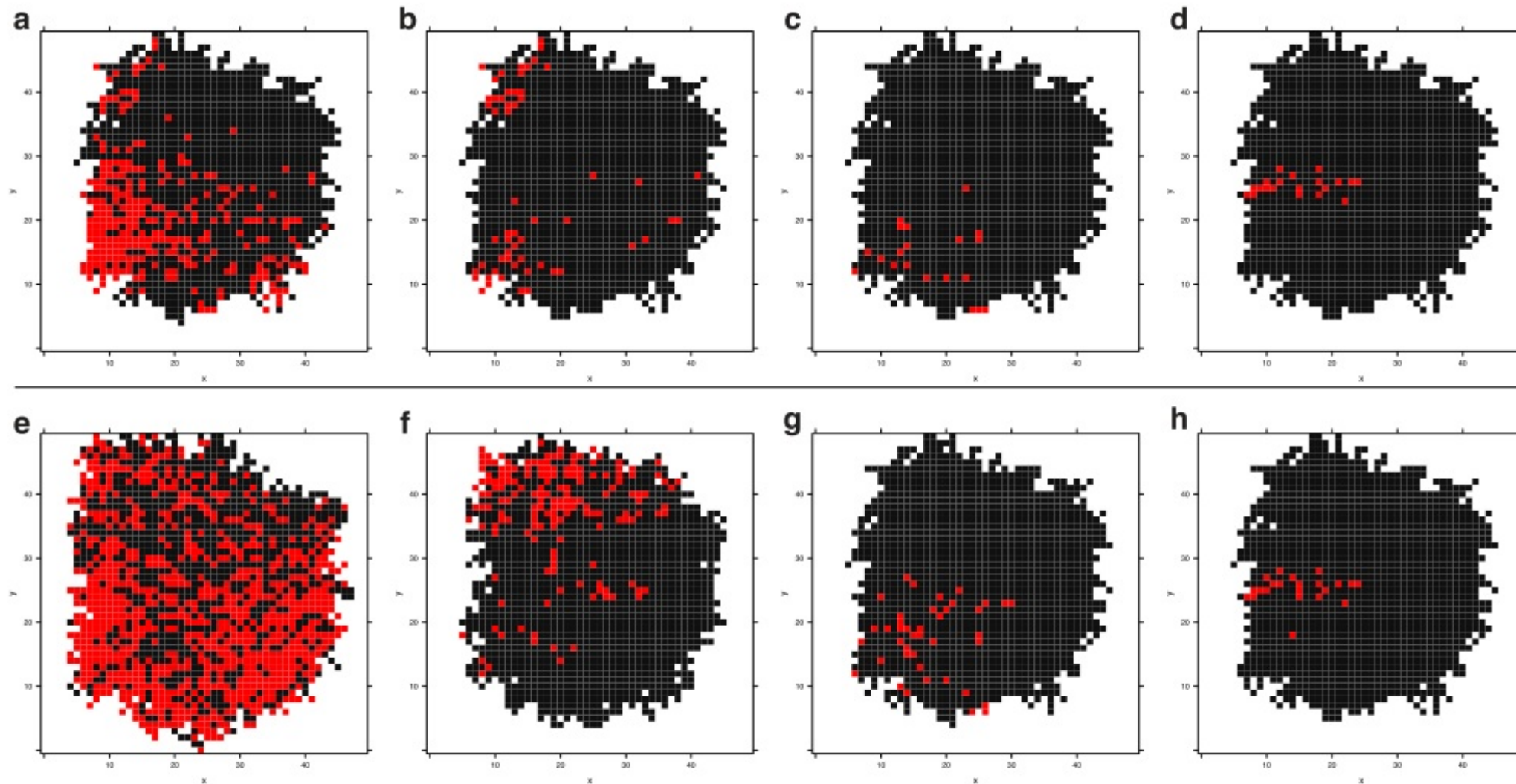
- 400x400x400 lattice
- Starting from a single gland until 80M reached
- Sampling regions
- ABC to fit observed data

Sottoriva 2015 (Big Bang in CRC)



Sottoriva 2015 (Big Bang in CRC)

- Neutral clone



Our interests

- Final goal is to do a general simulator of intratumoral population.
- Start with a simple model, including selection and genealogy of all the alleles/clones
- Define and separate fitness traits (proliferation speed, growth speed, adhesion)
- Different set of genes/mutations for different traits (pleiotropy?)

Limitations

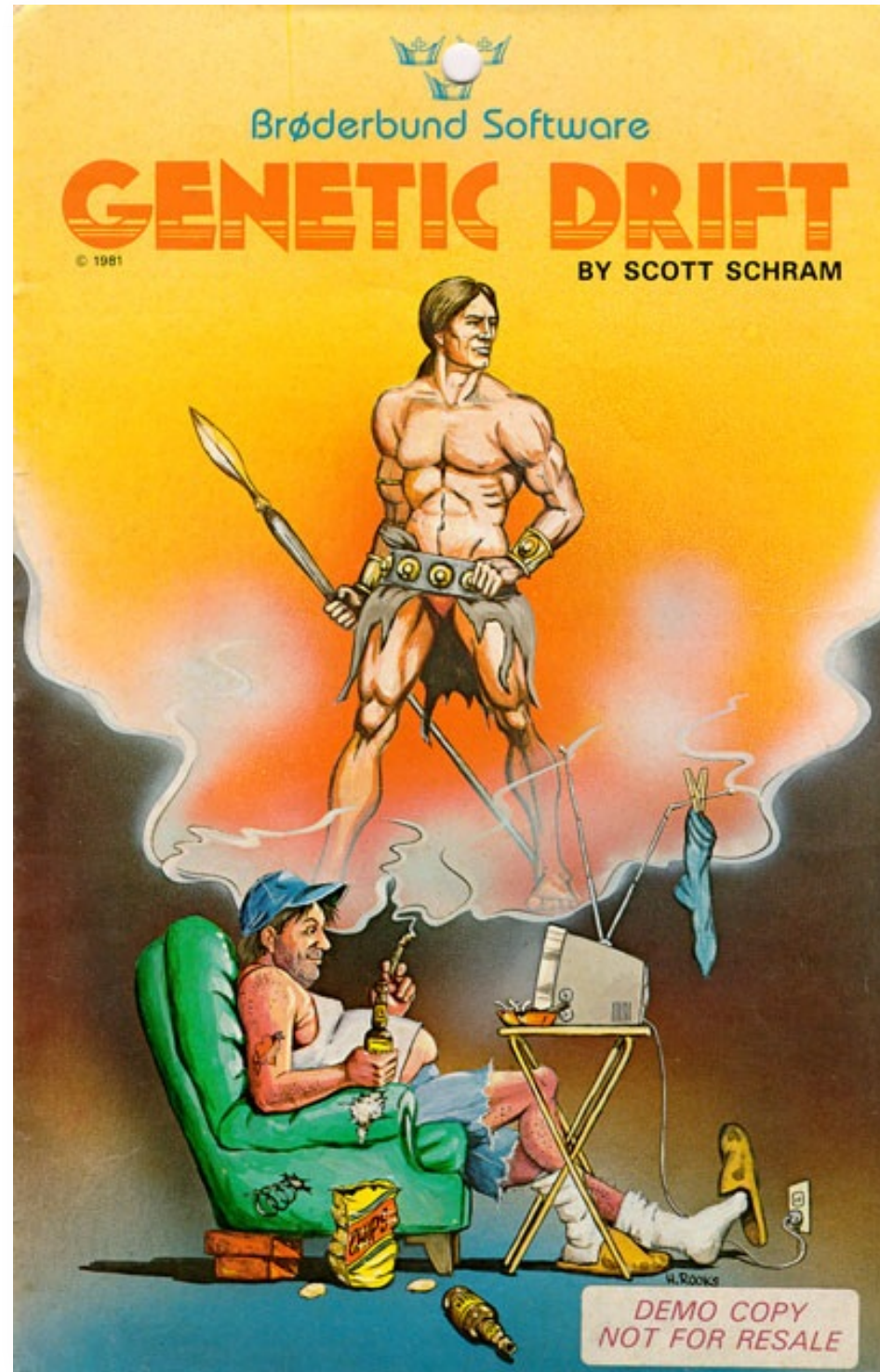
- Huge computational cost of ABMs
- Limited number of agents or time units
- Reduced genome representation

Further readings

Follow this link for a list of references for this talk:

<http://bit.ly/1TmtseB>

Thanks for coming



Presentation made with reveal.js. Get source at:
<https://github.com/anpefi/slides-seminar-IBMsim>