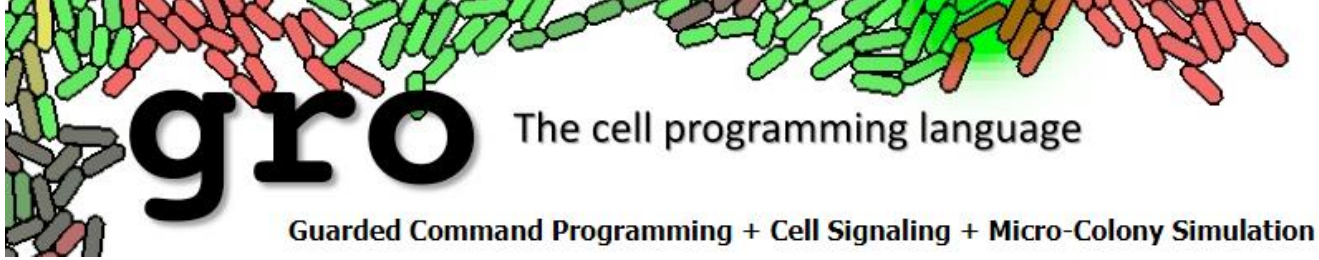
Gro Programming and Simulation:

BE 240 Lecture 6

Cindy Ren

05/14/2020

What is gro

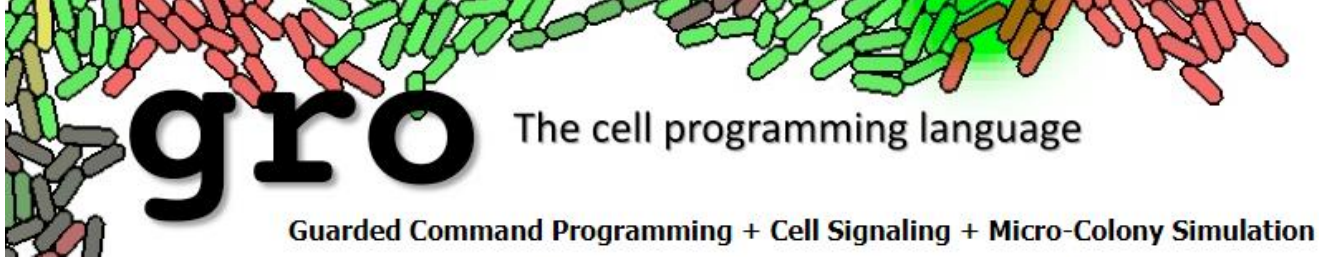


A tool for the simulation of multicellular behaviors in a 2D environment.

- **Cell growth/division**
- **Cell crowding**
- **Signal diffusion**
- **Molecular reactions (stochastic)**

- **Multi-levels of programming**
- **Growth control**
- **Well-mixed vs spatial**

What is gro



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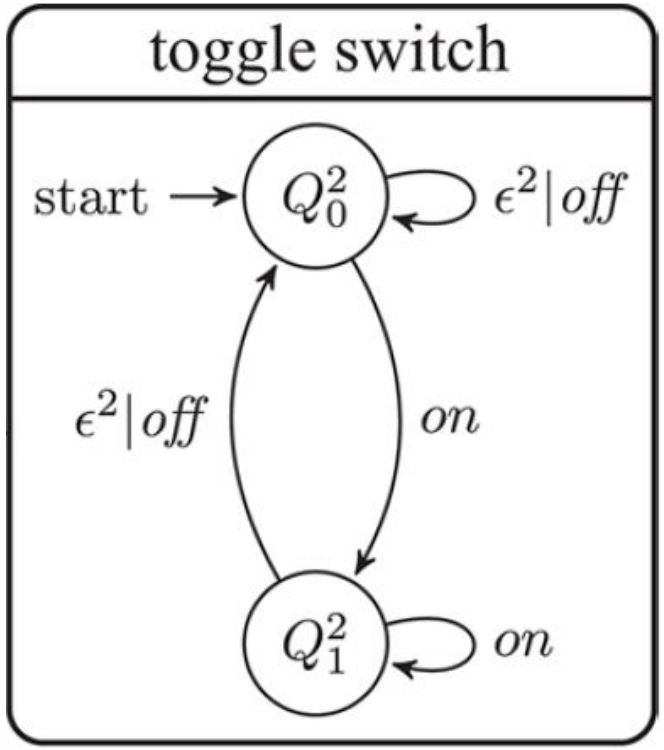
Levels of modeling

- Gro allows behaviors to be specified at whatever level of abstraction makes sense: from **high level code of logic**, to **low level biomolecular interactions**.
- First try for complicated temporal/spatial dynamics.
- **Finite state machines**: abstraction of biomolecular reactions



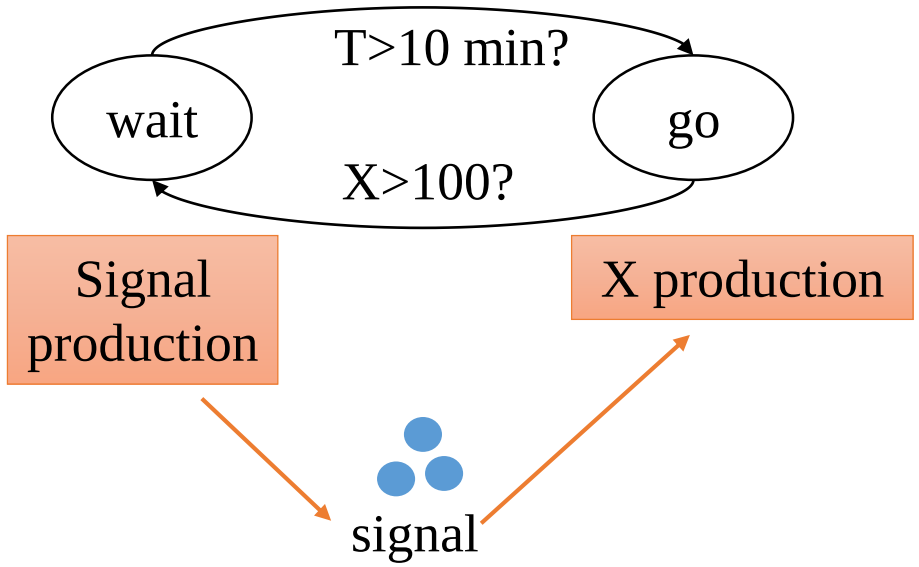
Levels of modeling: coupled oscillation coupled_oscillator.gro

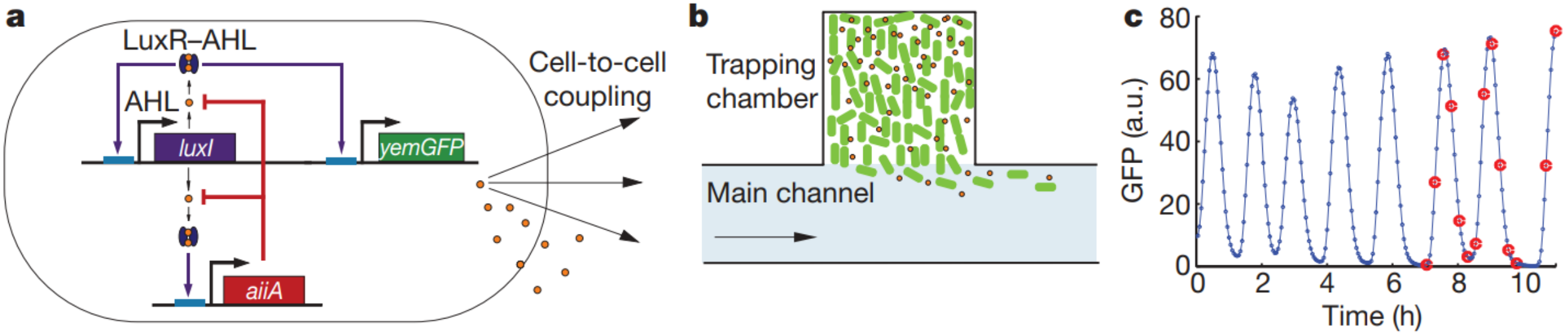
nature Vol 463 | 21 January 2010 | doi:10.1038/nature08753

ARTICLES

A synchronized quorum of genetic clocks

Tal Danino[1]*, Octavio Mondragón-Palomino[1]*, Lev Tsimring[2] & Jeff Hasty[1,2,3]





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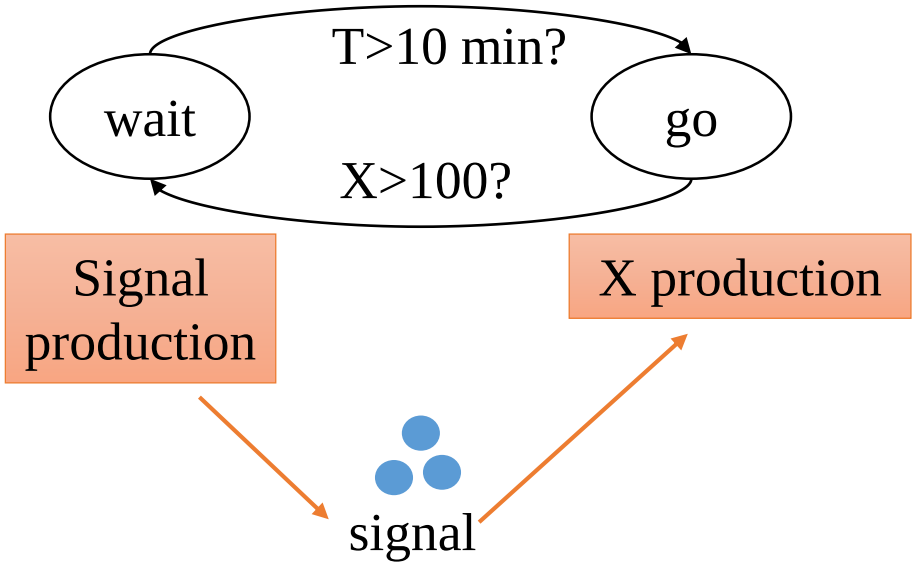
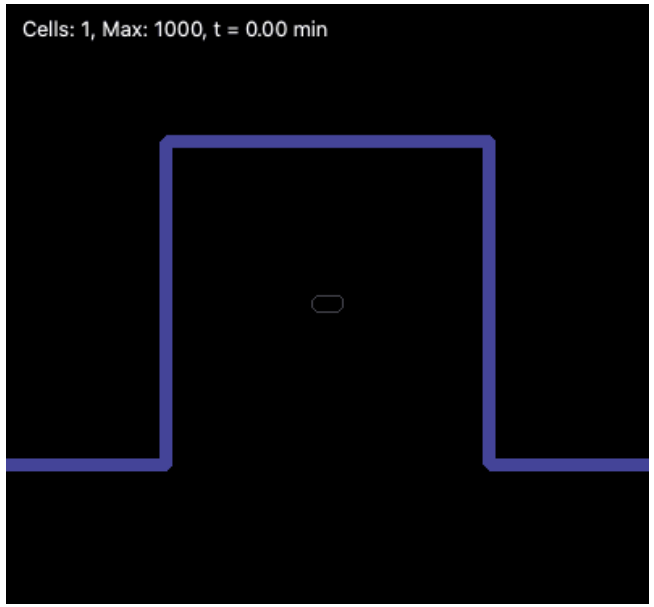
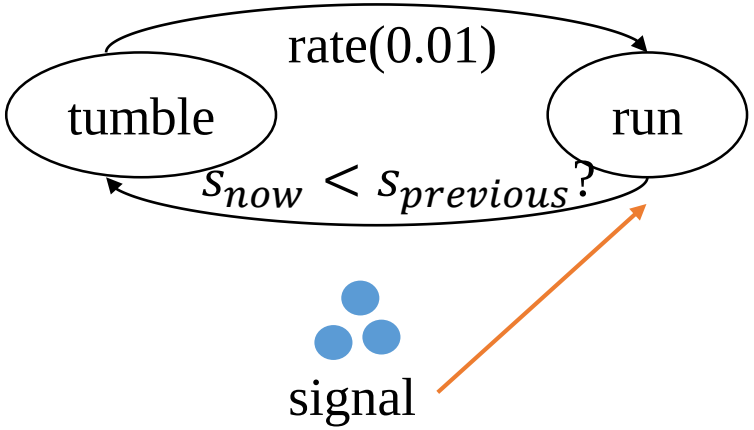




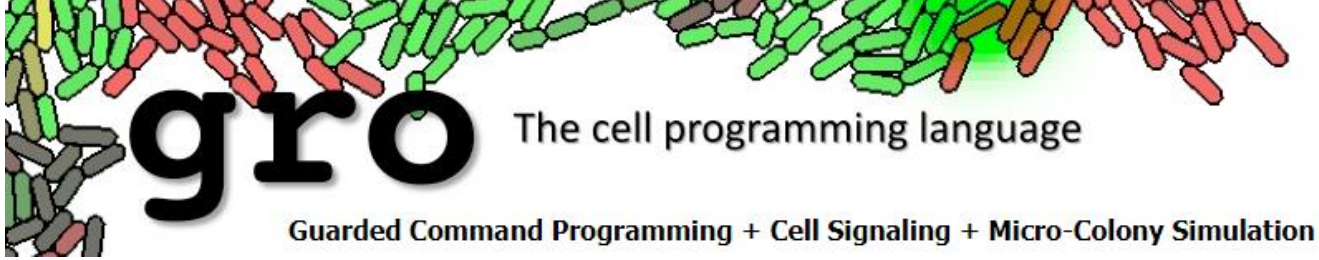

```
program oscillator(g0) := {
  gfp := 0.5*volume*g0;
  p := [mode := GO, t := 0, x := g0];
  true : {gfp := 0.5*volume * p.x}
  // advance the oscillation phase
  p.mode = GO & rate (k0) : {p.x := p.x + 0.01*(150-p.x)}
  p.mode = GO & rate(kb*get_signal(s)) : {p.x := p.x + 0.01*(150-p.x)}
  // phase reset
  p.x > 100 : {
    p.x := 0,
    p.mode := WAIT,
    emit_signal(s, se)
  }
  // refractory period timer
  p.mode = WAIT : {p.t := p.t+dt}
  p.mode = WAIT & p.t > tr : {
    p.mode := GO,
    p.t := 0
  }
};
```

Levels of modeling: chemotaxis chemotaxis.gro




```
program p() := {

  set ( "ecoli_growth_rate", 0.0 );
  m1 := 0;
  m2 := 0;
  t := 0;
  mode := 0;

  t > 0.25 : {
    t := 0,
    m1 := m2,
    m2 := get_signal(s)
  }

  mode = 0 : { run ( 8 ) }
  mode = 1 : { tumble ( 800 ) }

  mode = 0 & m2 < m1 & rate ( 0.5 ) : { mode := 1 }
  mode = 0 & m2 > m1 & rate ( 0.01 ) : { mode := 1 }

  mode = 1 & rate ( 0.01 ) : { mode := 0 }

  true : { t := t + dt }

};
```

What is gro



A tool for the simulation of multicellular behaviors in a 2D environment.

- Cell growth/division
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- Multi-levels of programming
- **Growth control**
- Well-mixed vs spatial

Easy for growth control circuits

- Gro has growth, division and death features and automatically updates cell volume. It also mimics the spread of microcolonies.

- Growth

```
set ( "ecoli_growth_rate", 0.0346574 );   // reactions/min
set ( "ecoli_init_size", 1.57 );          // fL
set ( "ecoli_division_size_mean", 3.14 ); // fL
set ( "ecoli_division_size_var", 0.005 ); // fL
set ( "ecoli_diameter", 1.0 );            // fL
```

- Death

```
rate (dC): { die() }
```

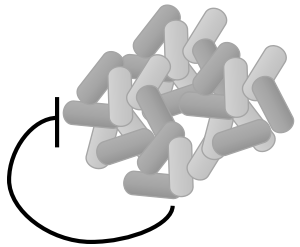
Same ODE model: $\frac{dN}{dt} = kN - dN$

Different behaviors

Growth control: growth rate

```
fun rep x . 2 / ( 2+ x^2 );

program growth() := {
  gfp := 100*volume;
  Sget := get_signal( S );

  true  : {
    gfp := 100*volume;
    emit_signal( S, kS );
    Sget := get_signal( S );
    set ( "ecoli_growth_rate", k*(rep Sget));
  };
}
```

slow down the growth

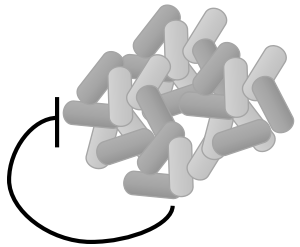


Growth control: death rate (lysed)

```
fun act x . x^2 / ( 2 + x^2 );

program lyse() := {
  gfp := 100*volume;
  Sget := get_signal( S );

  true  : {
    gfp := 100*volume;
    emit_signal( S, kS );
    Sget := get_signal( S );
  };

  rate( d* (act Sget) ) : {
    die();
  };
}
```

Cells: 1, Max: 2000, t = 1.56 min

increase the death



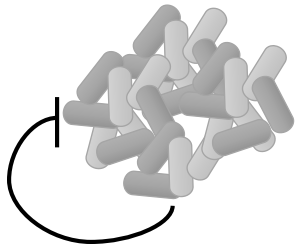
signal

Growth control: death rate (not lysed)

```
fun act x . x^2 / ( 2 + x^2 );

program death() := {
  gfp := 100*volume;
  Sget := get_signal( S );
  state:= [alive := 1];

  (state.alive = 1)  : {
    gfp := 100*volume;
    emit_signal( S, kS );
    Sget := get_signal( S );
  };

  rate( dC * (act Sget)  ) : {
    state.alive := 0;
    gfp := 2*volume;
    set("ecoli_growth_rate",0);
  };
};
```

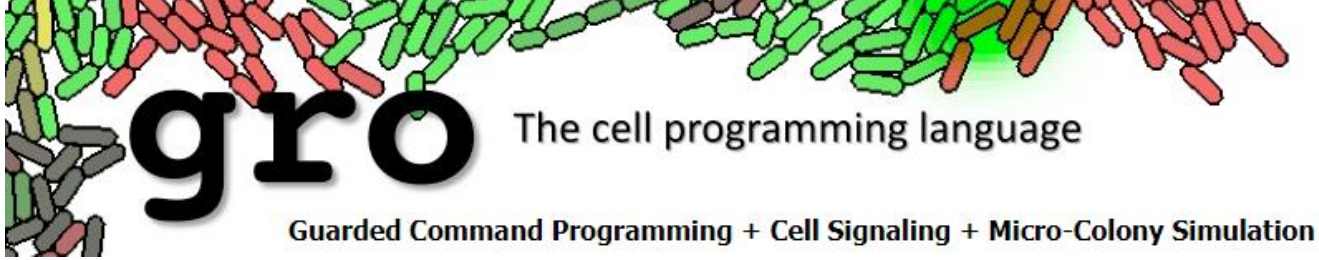
Cells: 1, Max: 2000, t = 1.60 min

increase the death



signal

What is gro



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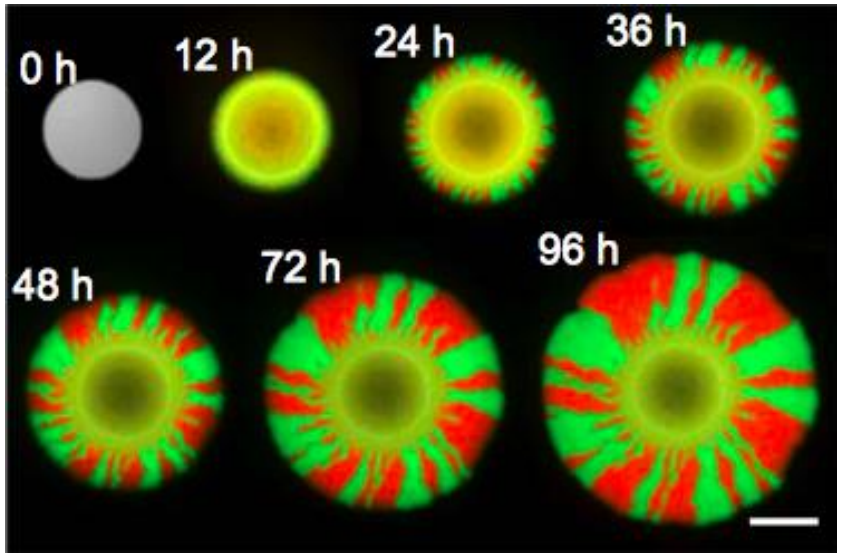
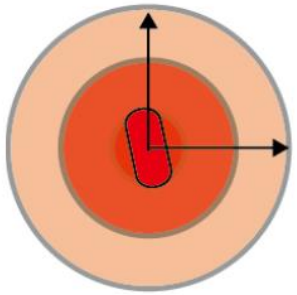
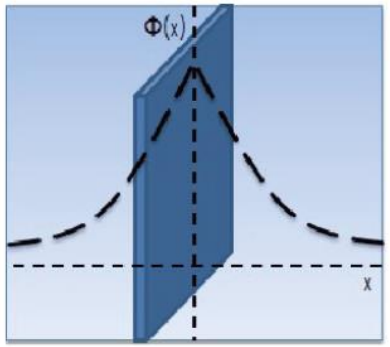
Well-mixed vs spatial assumptions

- **Cell growth** → expand microcolonies →self-organize into patterns
- **Signal diffusion** → only affect cells within the diffusion range
- **Environment heterogeneity** → cell behaviors affected by nutrients, antibiotics, oxygen…







Ozgen, Venhar Celik, et al. *Science advances* (2018).

Well-mixed vs spatial assumptions

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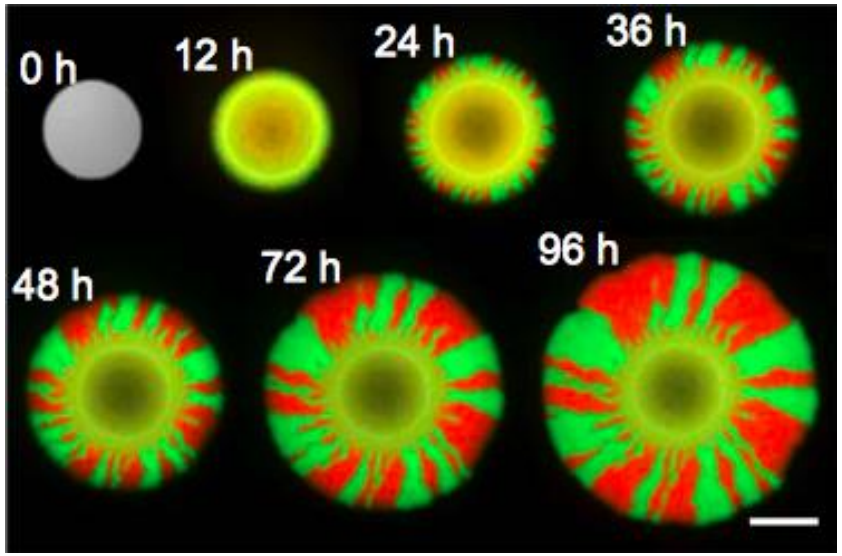

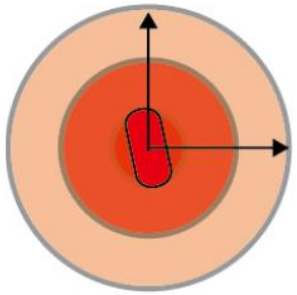

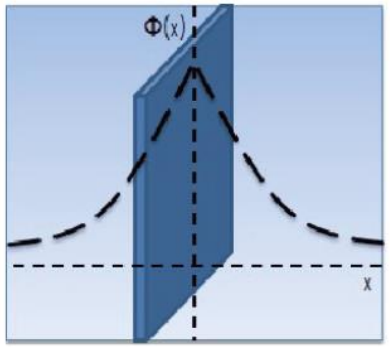

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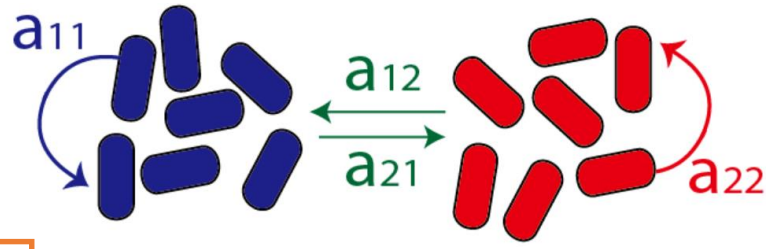
Cell growth: **patterning** depends on growth mechanisms

Interactions: activation/repression of growth/death



Cell-cell interactions

L-V Model

$$\frac{dC_1}{dt} = k_C\left(1 - \frac{C_1 + C_2}{C_{max}}\right)C_1 + \boxed{(a_{11}C_1 + a_{12}C_2)}C_1,$$

$$\frac{dC_2}{dt} = k_C\left(1 - \frac{C_1 + C_2}{C_{max}}\right)C_2 + \boxed{(a_{21}C_1 + a_{22}C_2)}C_2.$$

Same ODE model

Different mechanisms:

repression of growth = activation of death: $a < 0$

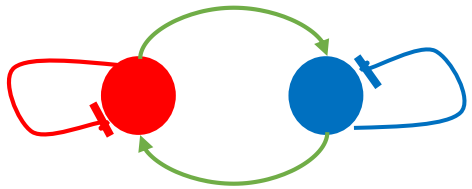
activation of growth = repression of death: $a > 0$

Different spatial behaviors

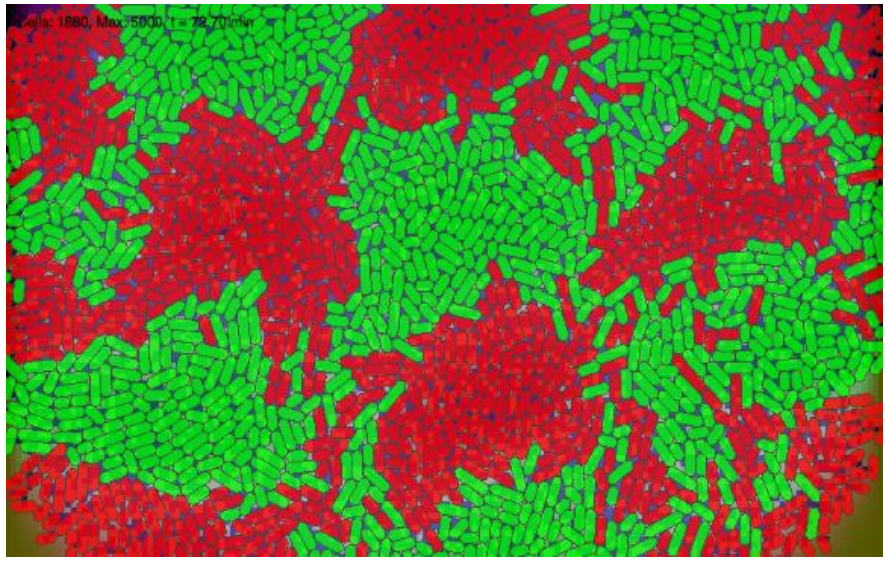
slow growth ≠ fast death (not lysed) ≠ fast death (lysed)

Cell growth: **patterning** depends on growth mechanisms

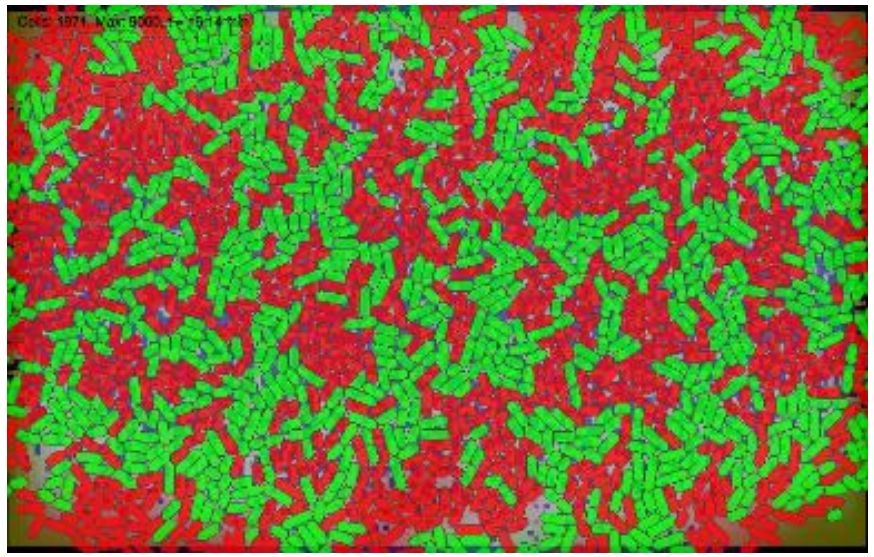
Cooperation: $a_{12} > 0, a_{21} > 0$



Activation/repression of growth

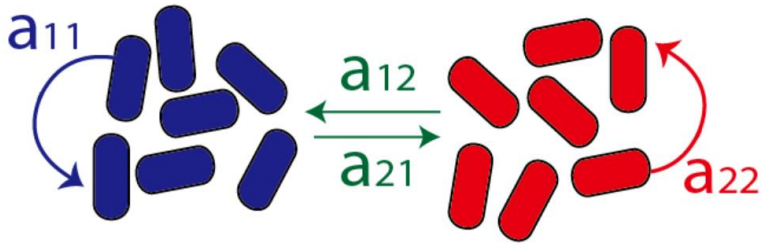


Repression/activation of death (lysed)



Cell growth: coexistence **stability** depends on interactions

Interactions: activation/repression of growth/death



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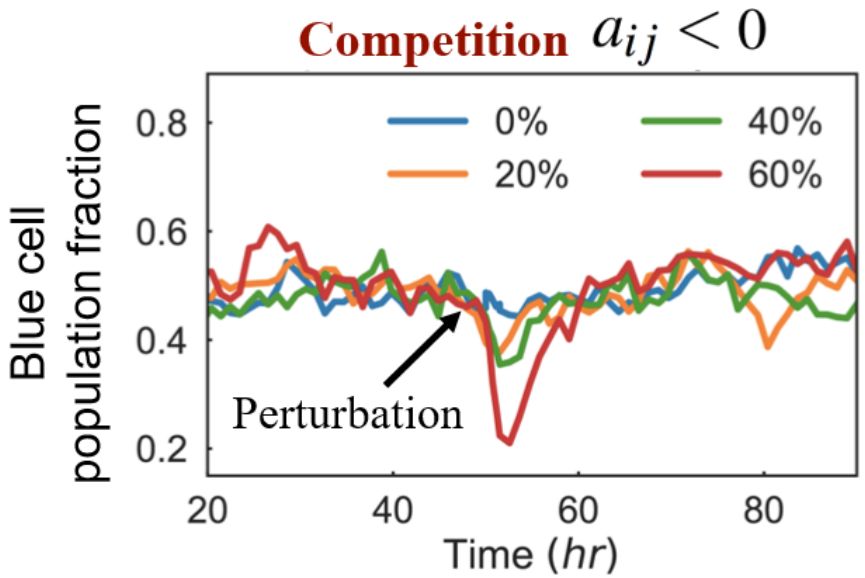
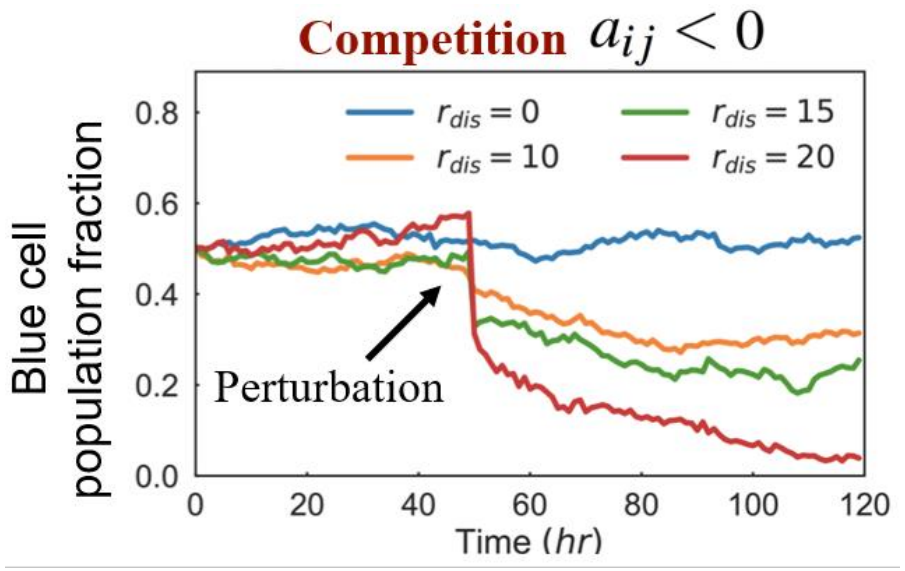
$$\frac{dC_2}{dt} = k_C\left(1 - \frac{C_1 + C_2}{C_{max}}\right)C_2 + (a_{21}C_1 + a_{22}C_2)C_2.$$

ODE model: stable coexistence

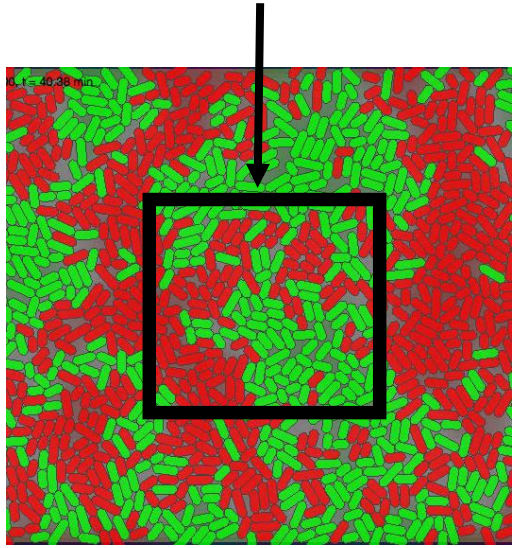


Spatial model: stable -> unstable



Cell growth: coexistence **stability** depends on interactions

Perturbation



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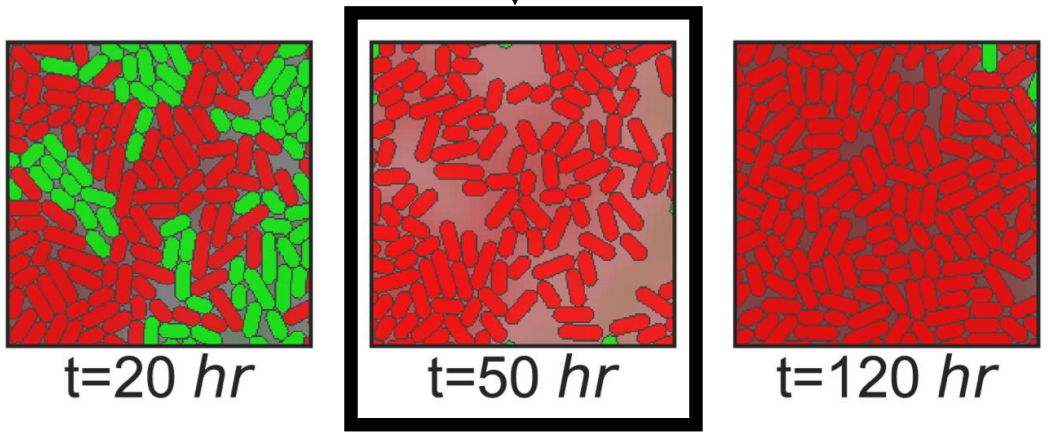
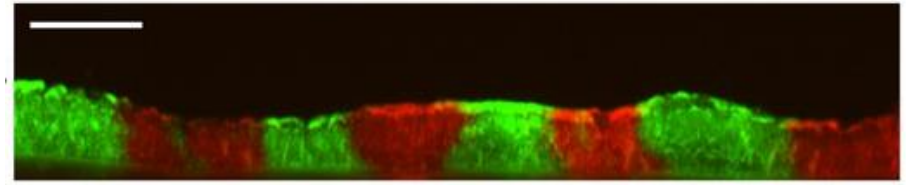
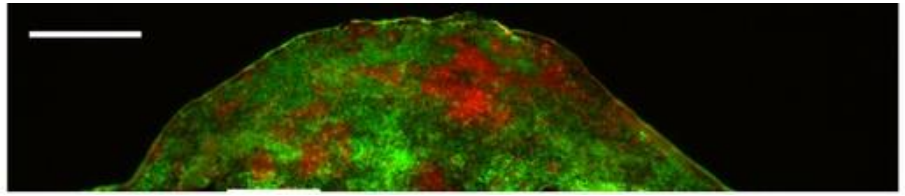


Competition



Segregated patterning

Cooperation



Intermixing patterning

Ren, X., & Murray, R. M. 2019 *ECC*
Momeni, Babak, et al. *Elife* 2 (2013).

Well-mixed vs spatial assumptions

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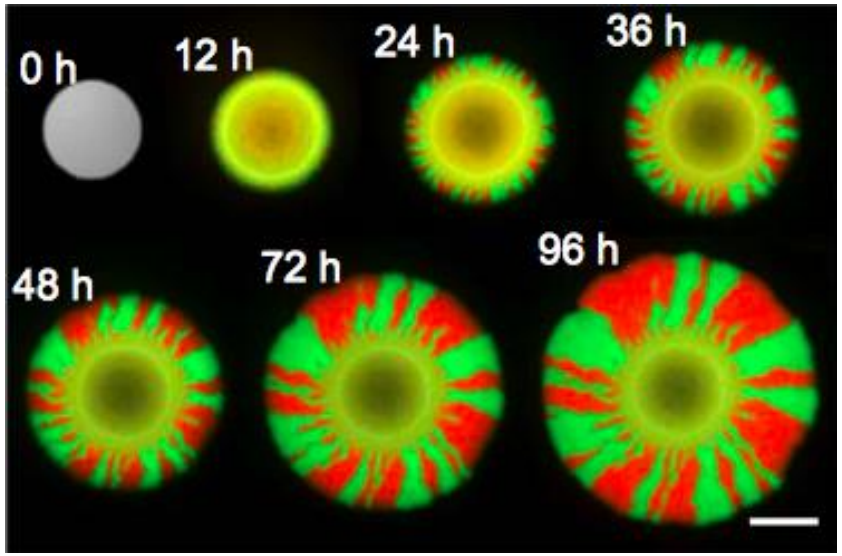
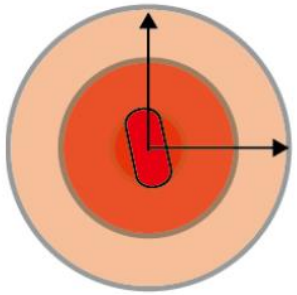
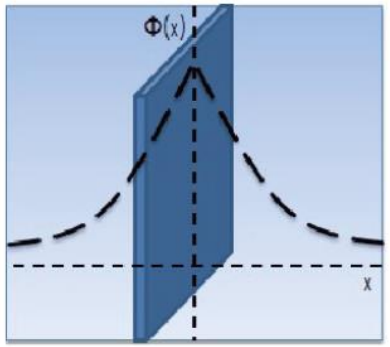


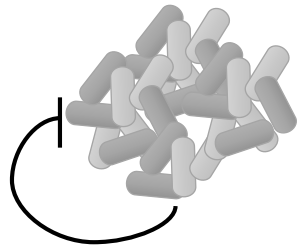




Ozgen, Venhar Celik, et al. *Science advances* (2018).

Signal diffusion: rate determines **strength**

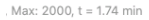
slow down the growth

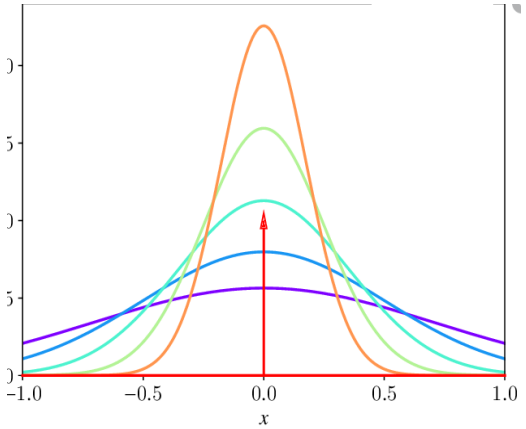


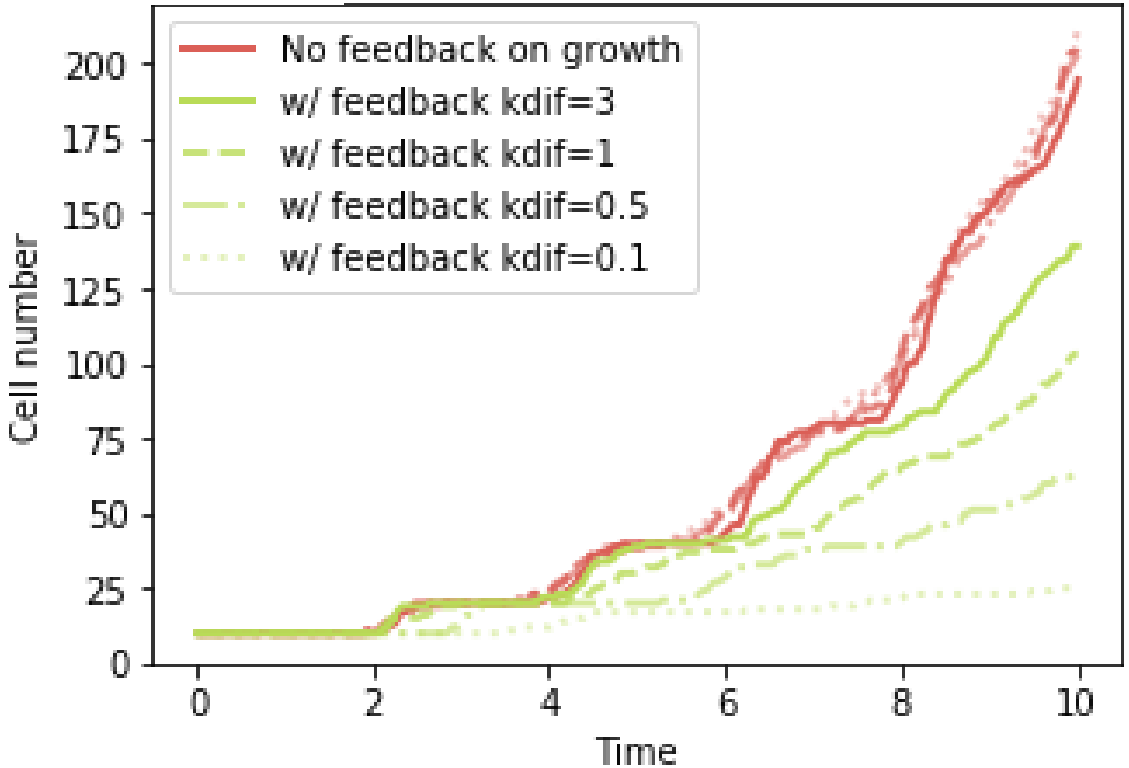
Growth control: growth rate

kdif=3

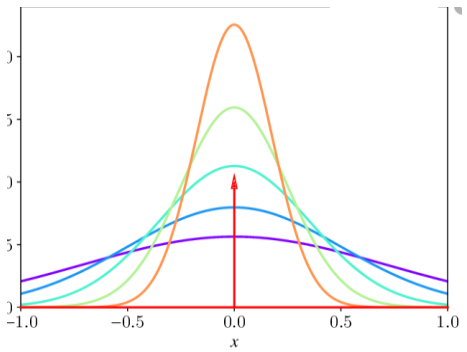
kdif=1



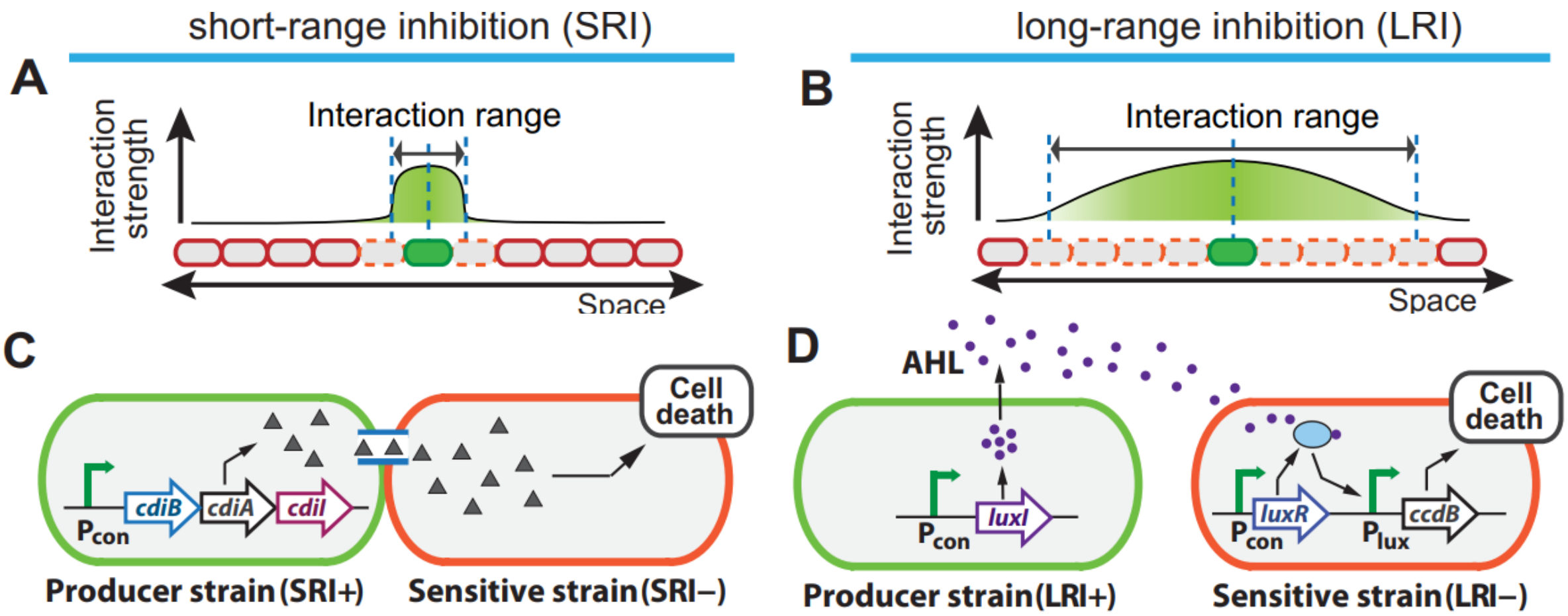




Signal diffusion: rate determines **range**



Green cells inhibit red cells



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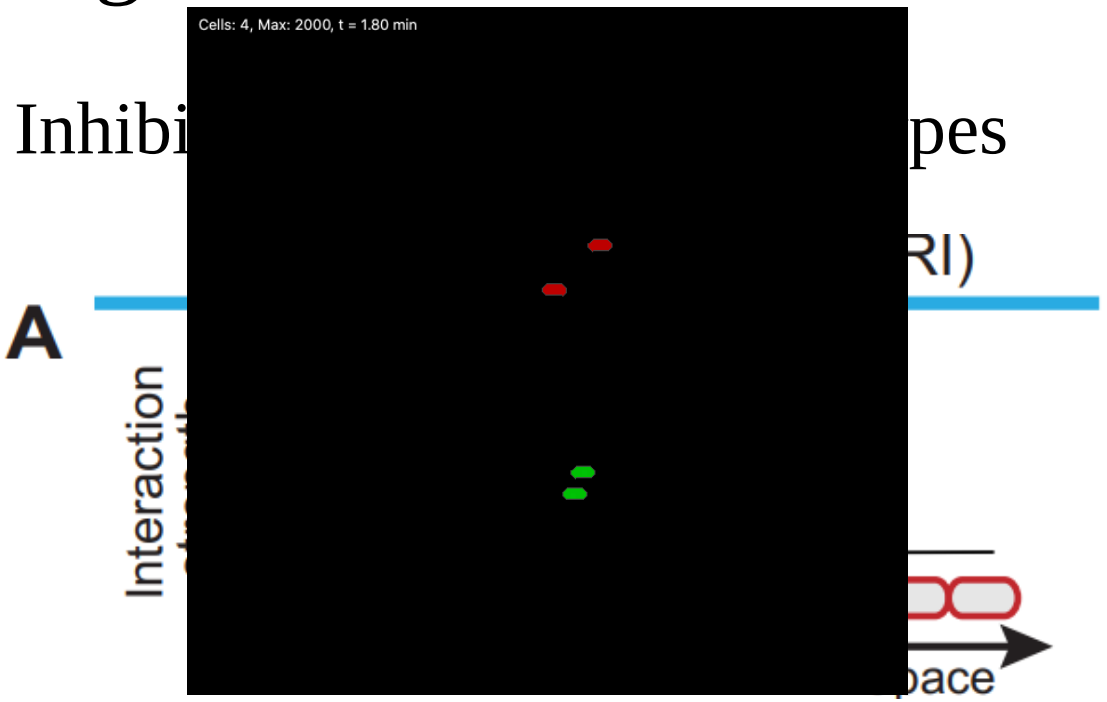
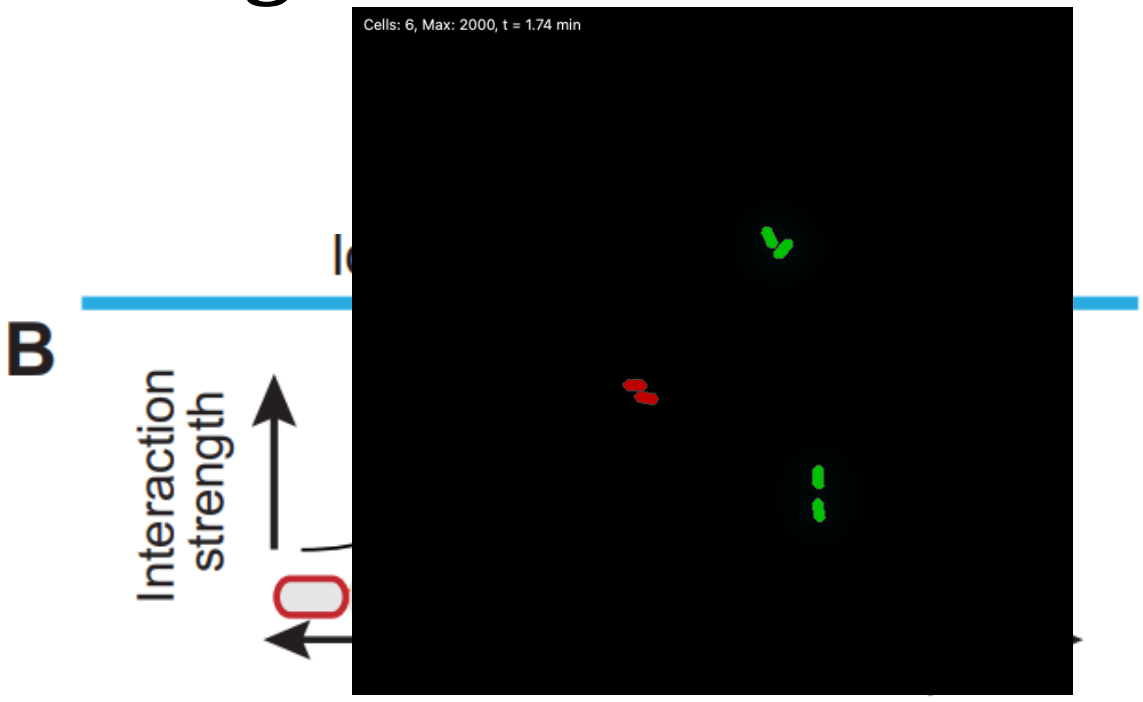
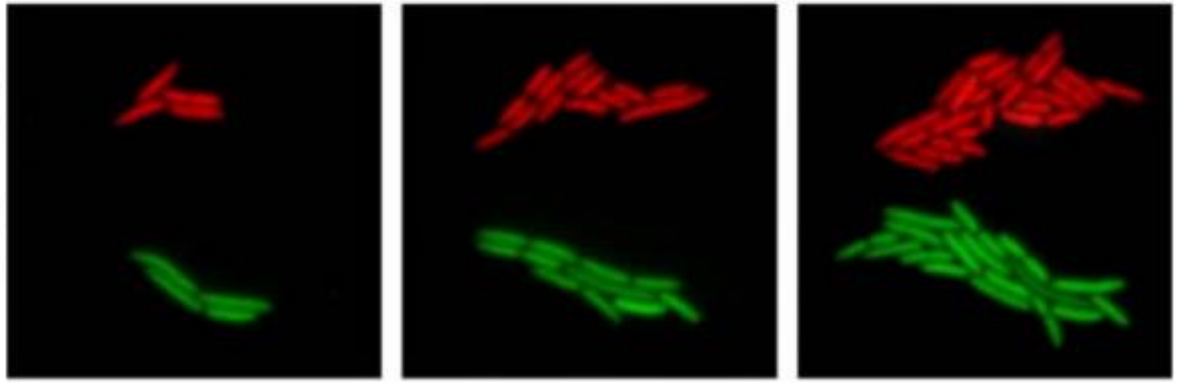
Signal diffusion: rate determines **range**

Inhibi pes





0 hr 1 hr 2 hr



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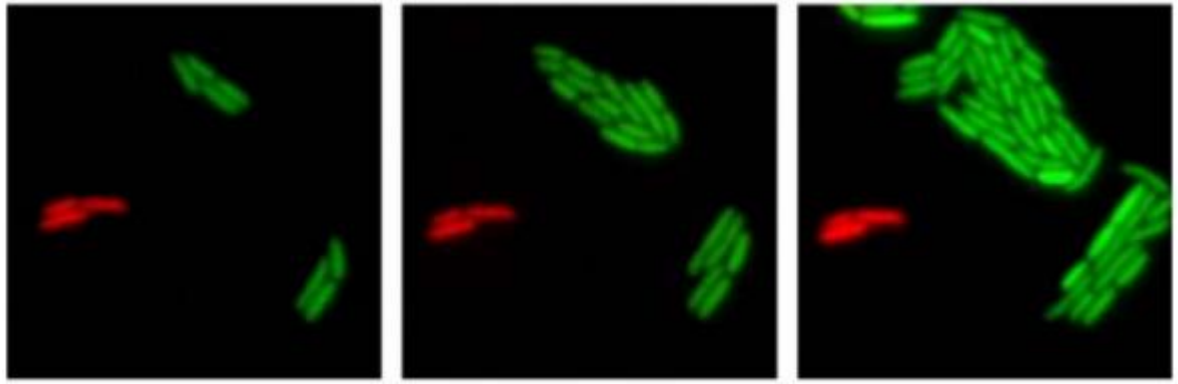

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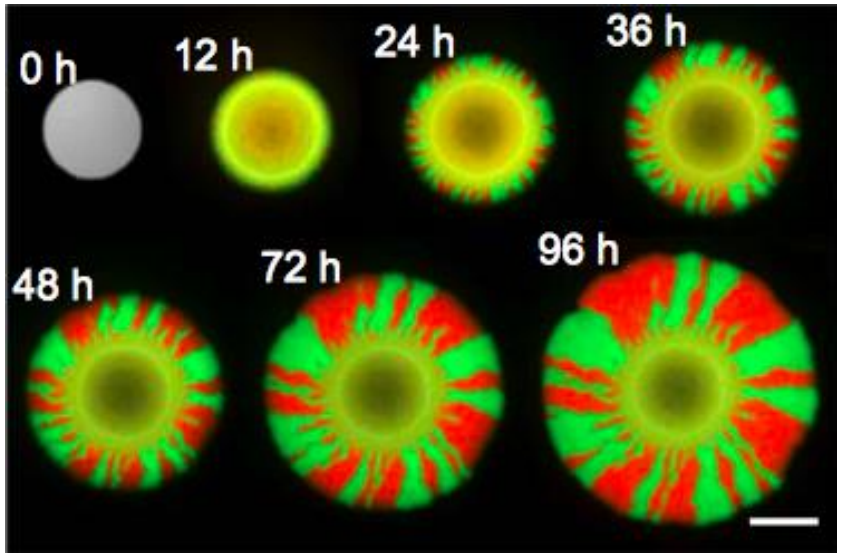
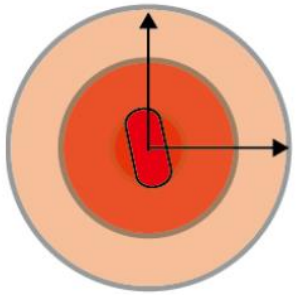
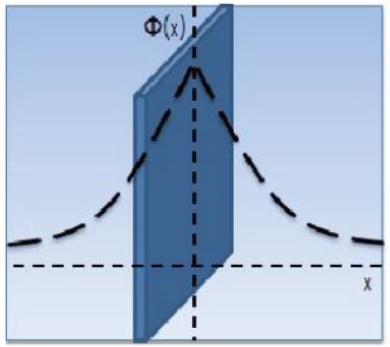
- **Signal diffusion** → only affect cells within the diffusion range

- **Environment heterogeneity** → cell behaviors depends on nutrients, antibiotics, oxygen…



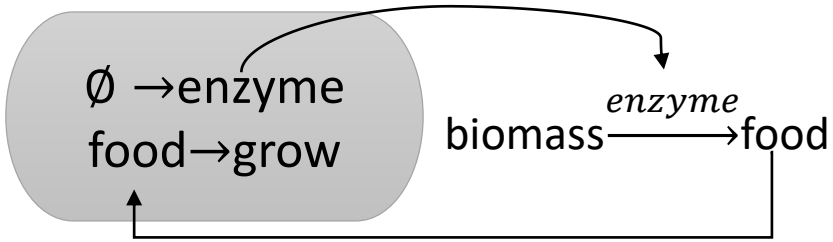


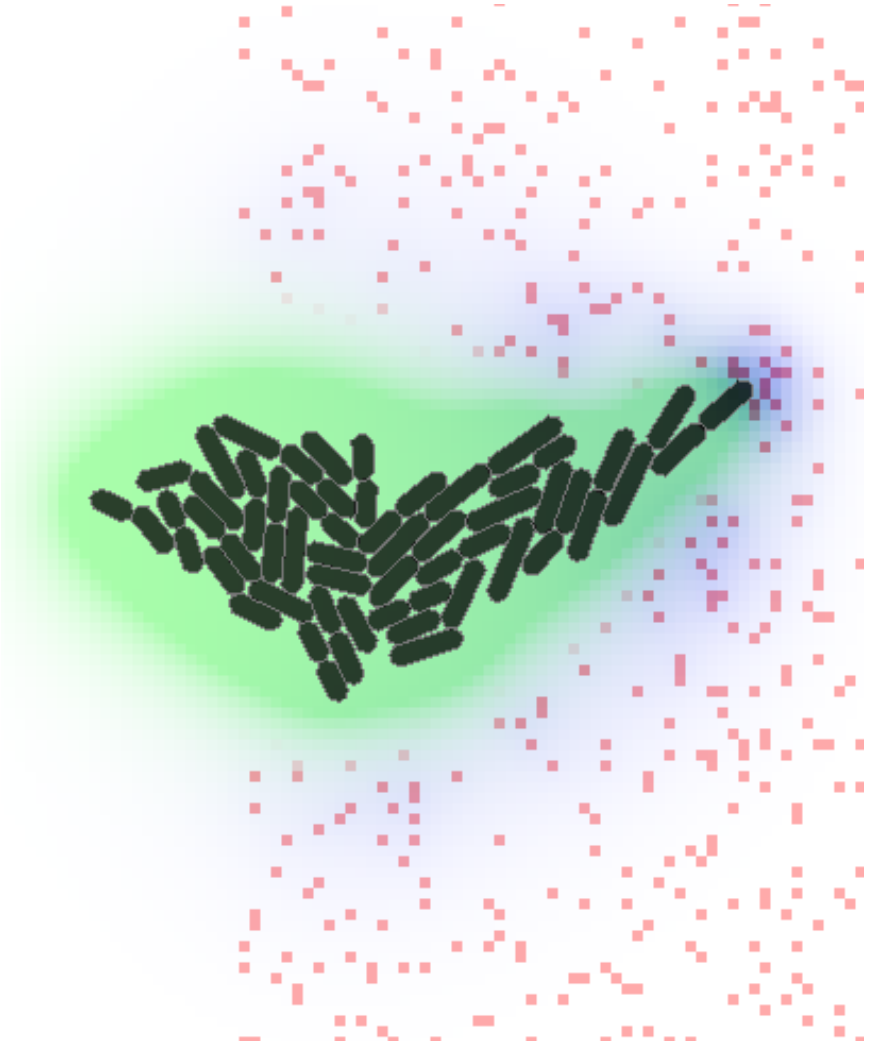


Ozgen, Venhar Celik, et al. *Science advances* (2018).

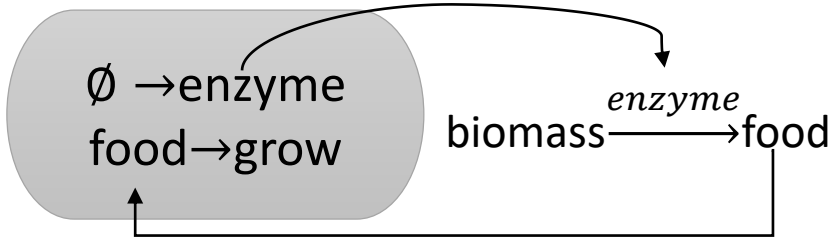
Environmental heterogeneity

Nutrient distribution





Environmental heterogeneity



- Bioprocessing

```
biomass := signal(0, 0);
enzyme := signal(4,0.3);
food := signal(5, 0.1);

reaction({biomass,enzyme},{food,enzyme},5);
set("ecoli_growth_rate",0.0);

program bioprocessor() := {
 true : {
 set("ecoli_growth_rate",get_signal(food)),
 emit_signal(enzyme,1)
 }
};

program main() := {
 t := 0;
 true: { t := t + dt }
 foreach i in range 500 do {
 set_signal(biomass,rand(300),(rand(500)-250),10)
 } end;
};
ecoli ( [], program bioprocessor() );
```

declare a signals (no diffusion or degradation for biomass)

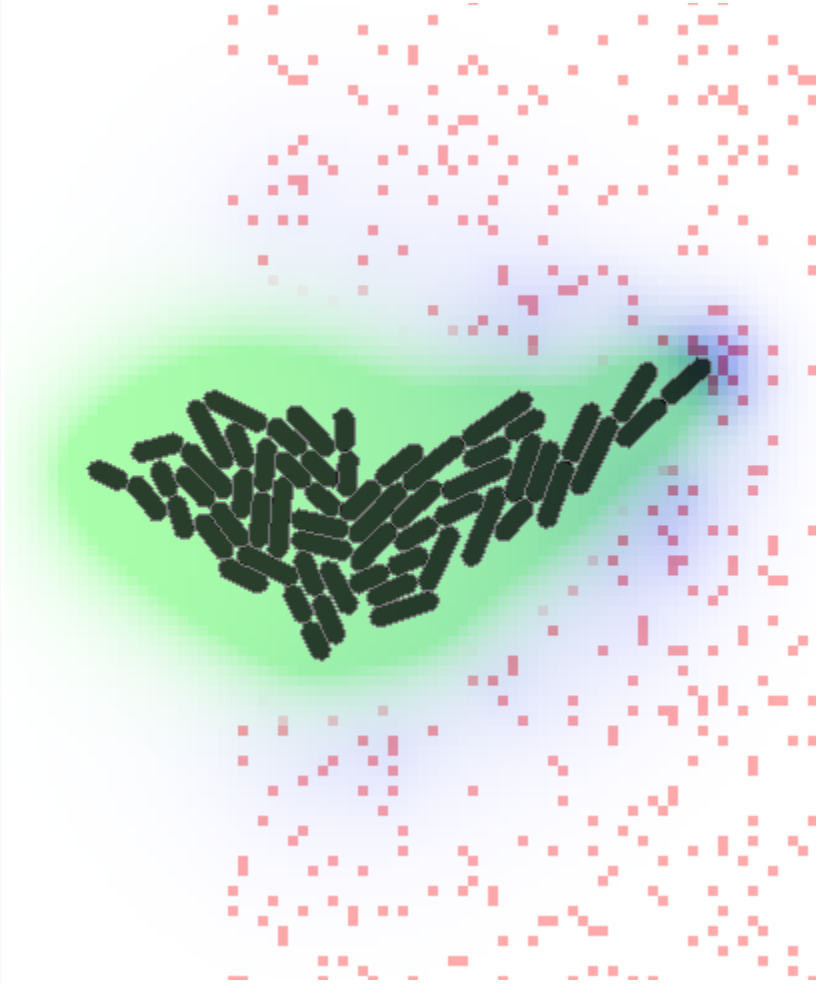
enzyme catalyzes biomass and generates food

set cell growth rate without food

cell growth depends on food

cell secrets enzymes

initializing biomass



What can we simulate with gro?

- **Gro programming at different levels**
  High level logic → biomolecular reactions

- **Growth control circuit with different mechanisms**
  Growth, death, lysis

- **Well-mixed vs spatial assumptions**
  Cell growth
  Signal diffusion
  Environment heterogeneity