KATHOLIEKE UNIVERSITEIT
LEUVEN

Modeling for Dr. Coli

a synthetic biology approach to intelligent bacterial drug delivery

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2008 iGEM team KULeuven

ECSB II

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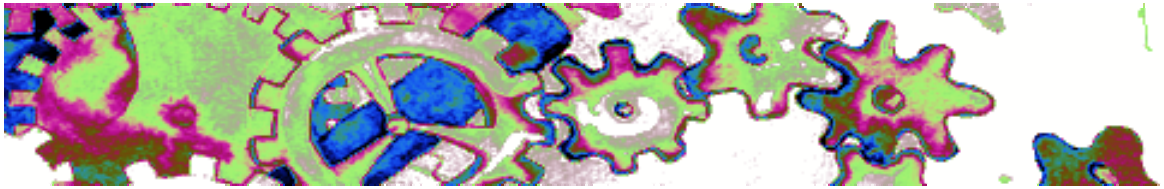
Centre of Microbial and Plant Genetics
Department of Microbial and Molecular Systems
K.U.Leuven - BioSCENTer

iGEM & BioBricks

- international **Genetically Engineered Machines** competition

- BioBricks: off the shelf DNA building blocks



Registry of Standard Biological Parts

intelligent bacterial drug delivery

Treatment of Murine Colitis by *Lactococcus lactis* Secreting Interleukin-10

Lothar Steidler,[1]*† Wolfgang Hans,[1]† Lieven Schotte,[1] Sabine Neirynck,[1] Florian Obermeier,[2] Werner Falk,[2] Walter Fiers,[1] Erik Remaut[1]

Science 2000

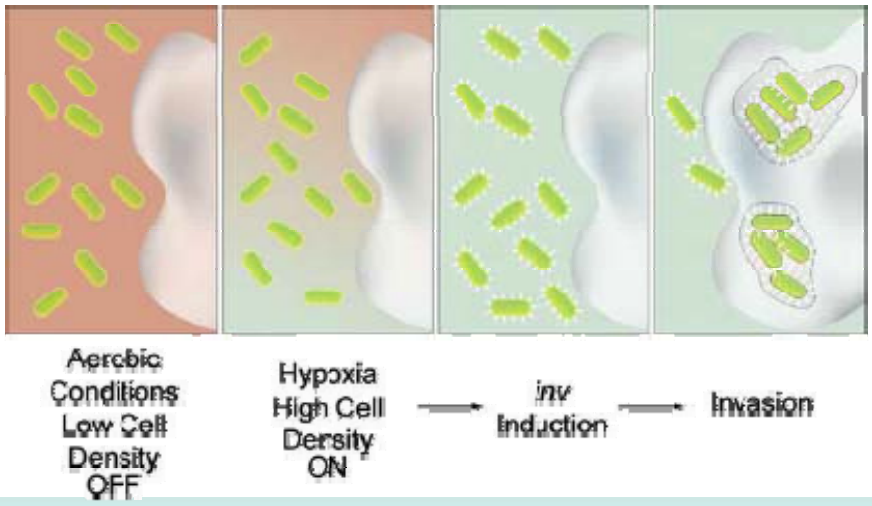
- *Lactococcus lactis* expressing human IL-10 to treat IBD (e.g. Crohn's disease)
- University of Ghent – VIB
- ActoGeniX: AG011 currently in Phase 2 clinical trial in ulcerative colitis patients

Environmentally Controlled Invasion of Cancer Cells by Engineered Bacteria

J. Christopher Anderson[1,3], Elizabeth J. Clarke[3], Adam P. Arkin[1,2*] and Christopher A. Voigt[2,3]

J Mol Biol 2006

E. coli with *Yersinia pseudotuburculosis* invasin under control of O_2 and QS responsive promoter



Dr. Coli

- **Dr. Coli delivers drugs *in situ***

  drug production when a disease signal is sensed:

  Input and Output

- **Dr. Coli self-destructs**

  when the patient is cured, Dr. Coli will eliminate itself from its host:

  InverTimer, Cell Death, Reset, Filter

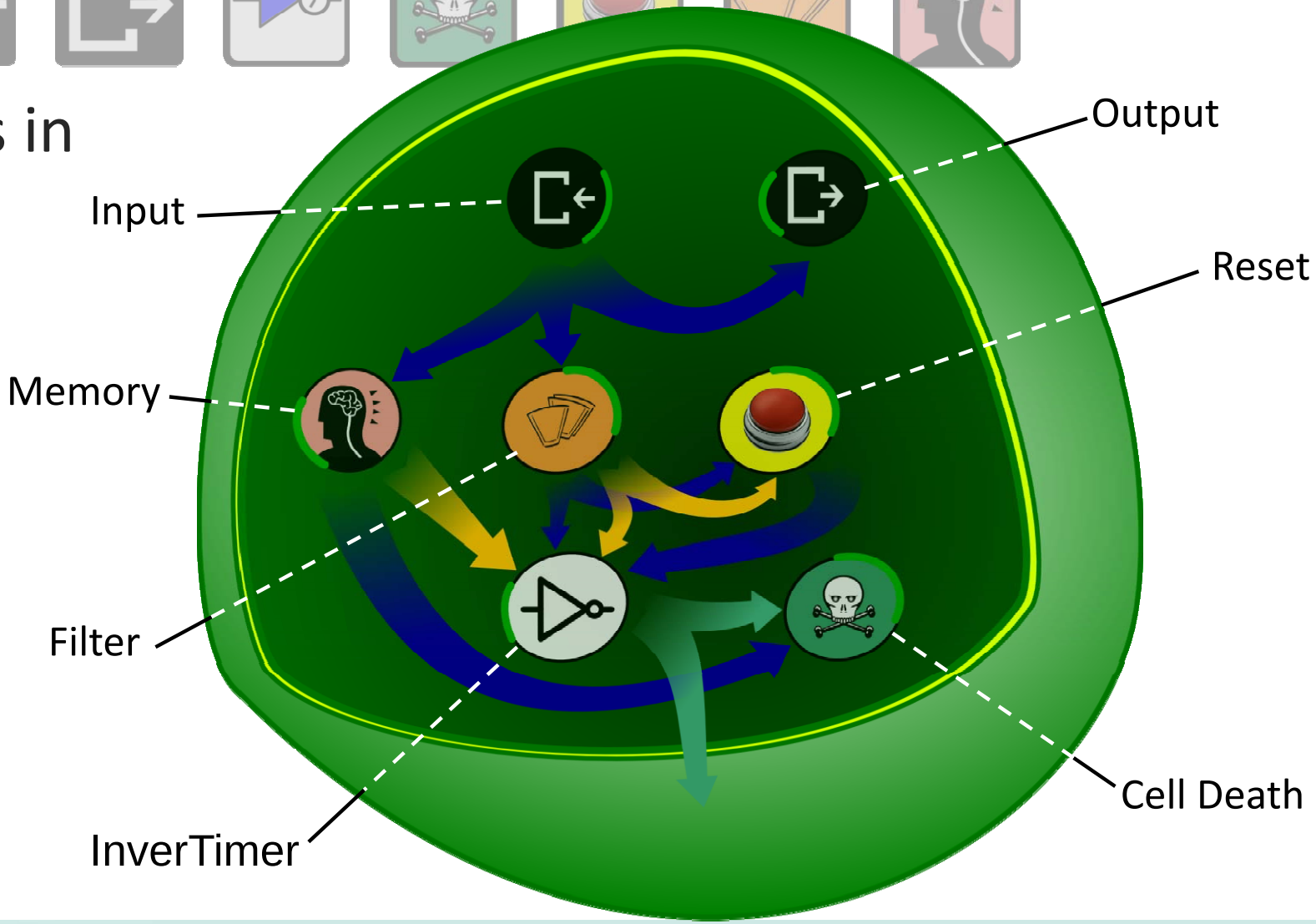
- **Dr. Coli in production**

  it should be possible to produce Dr. Coli without it self-destructing:

  Memory

Dr. Coli

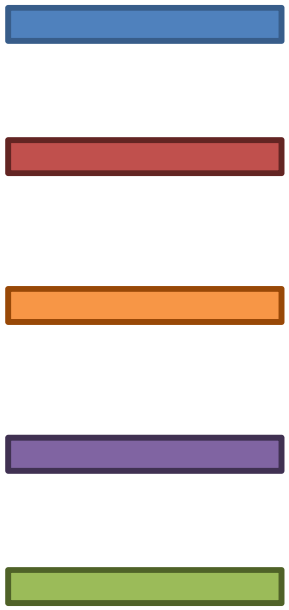
7 subsystems in
1 Dr. Coli



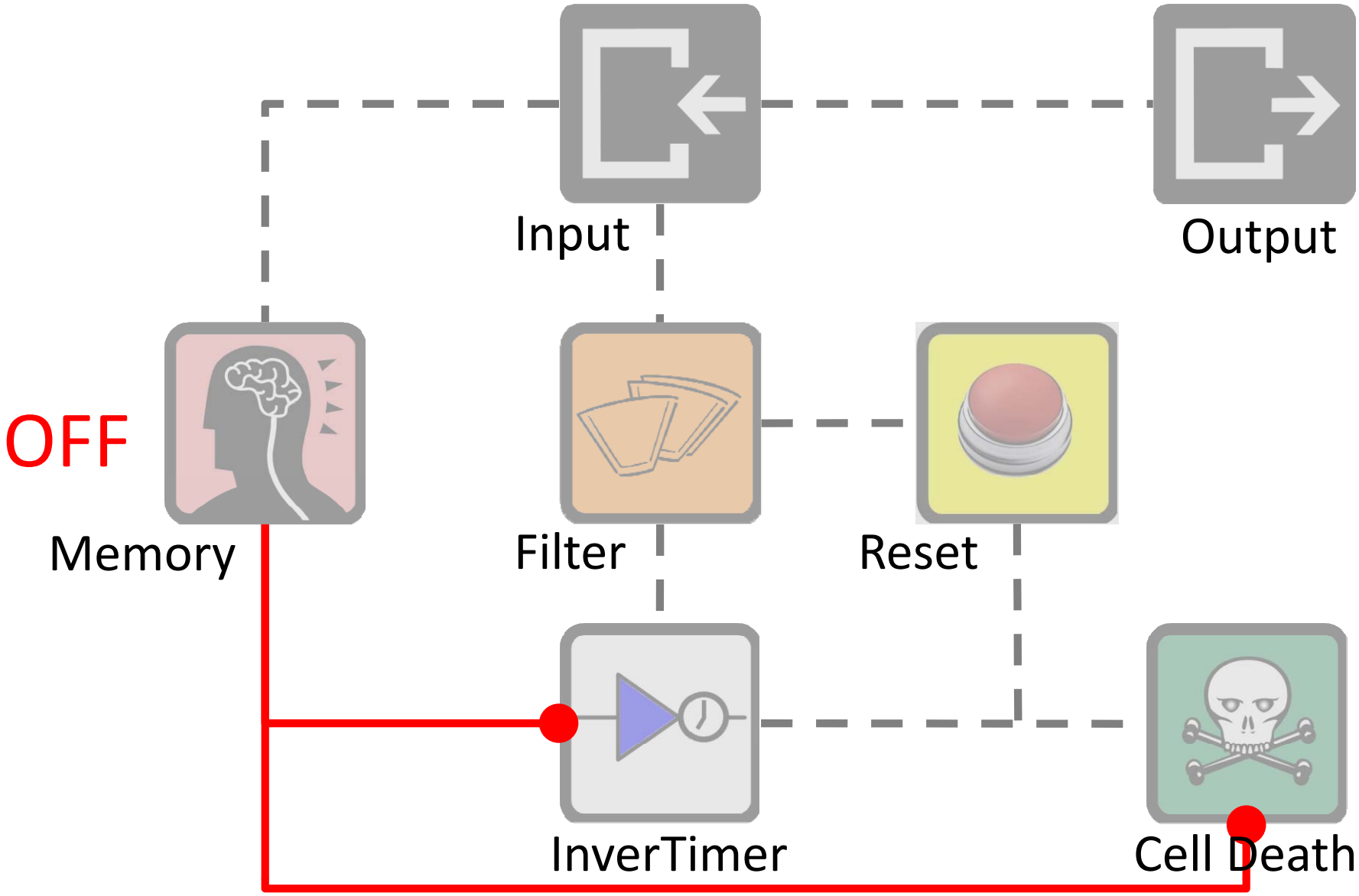
Dr. Coli @ work

Five different phases:

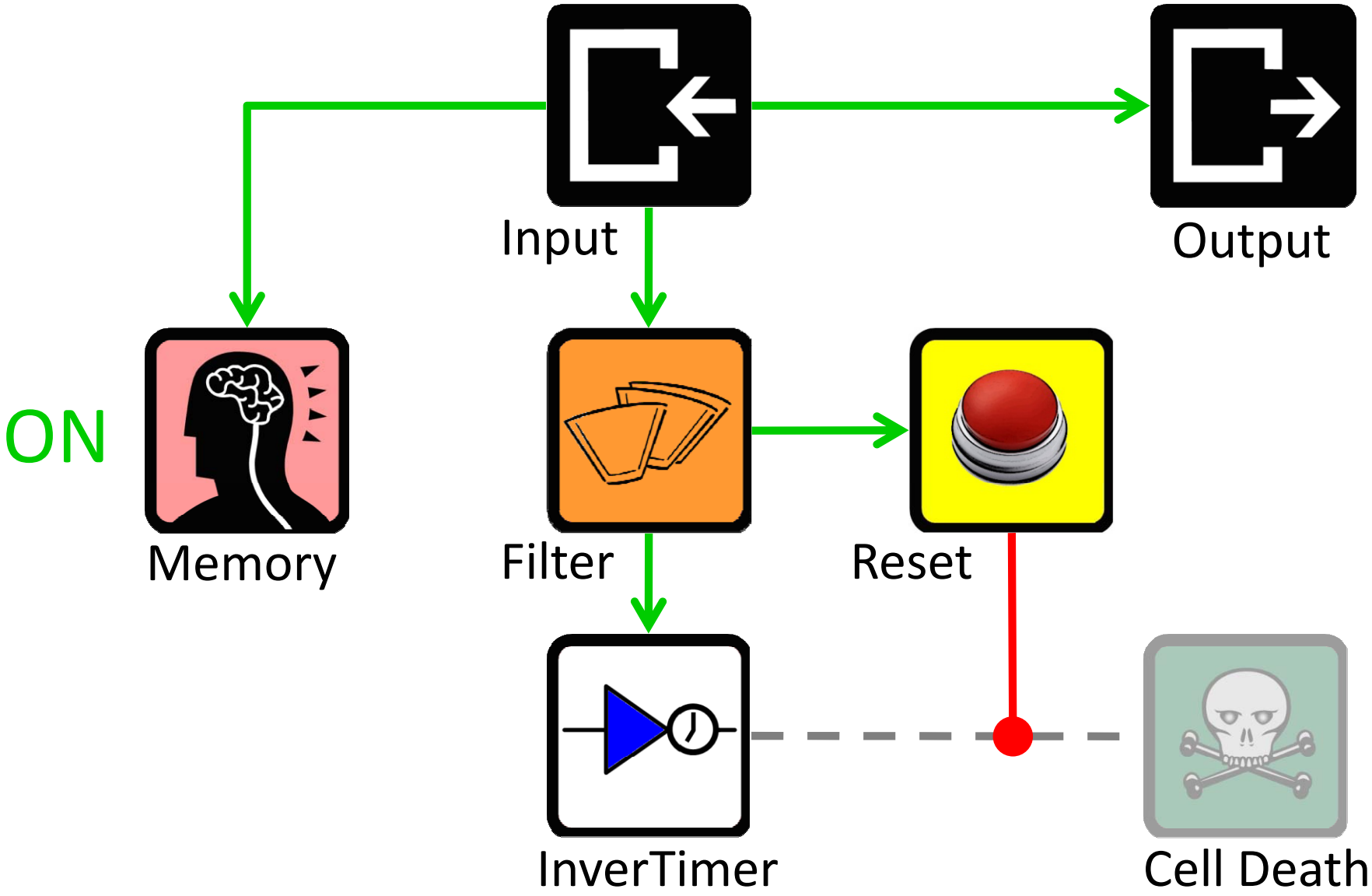
1. No disease signal
2. First disease signal
3. Temporarily/locally cured
4. Patient relapse
5. Patient cured



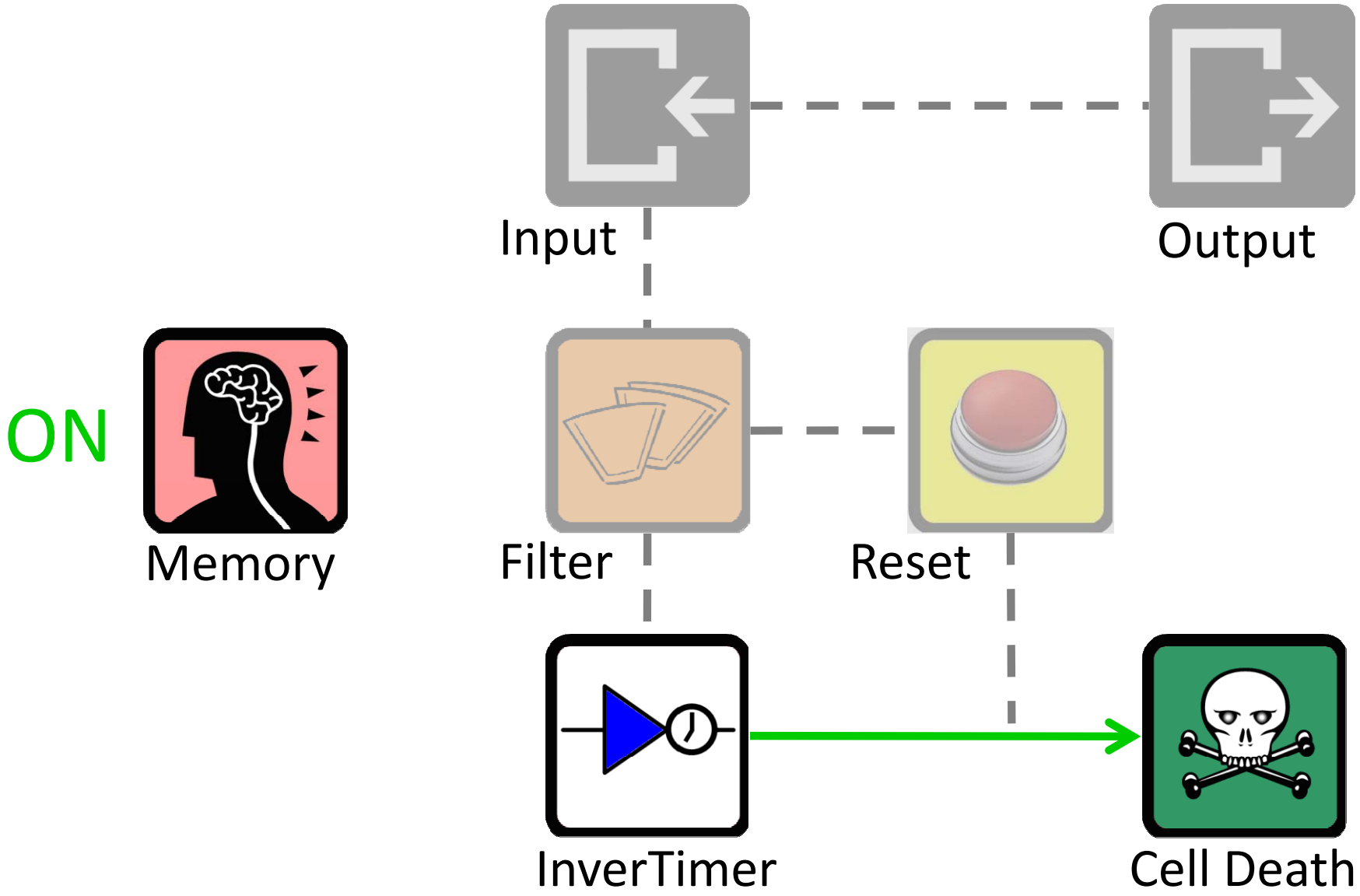
@ work 1: No Disease Signal



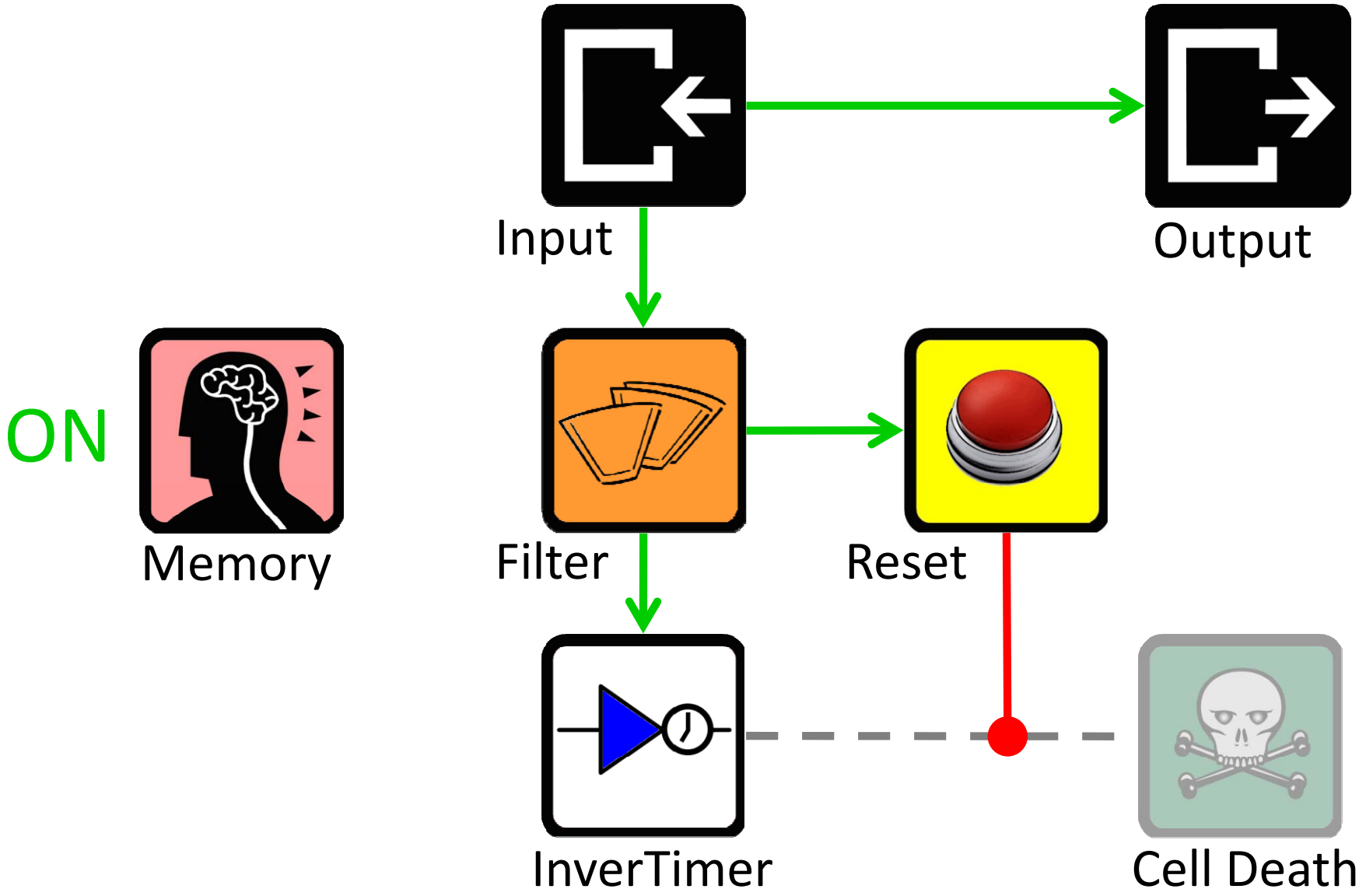
@ work 2: 1st Disease Signal



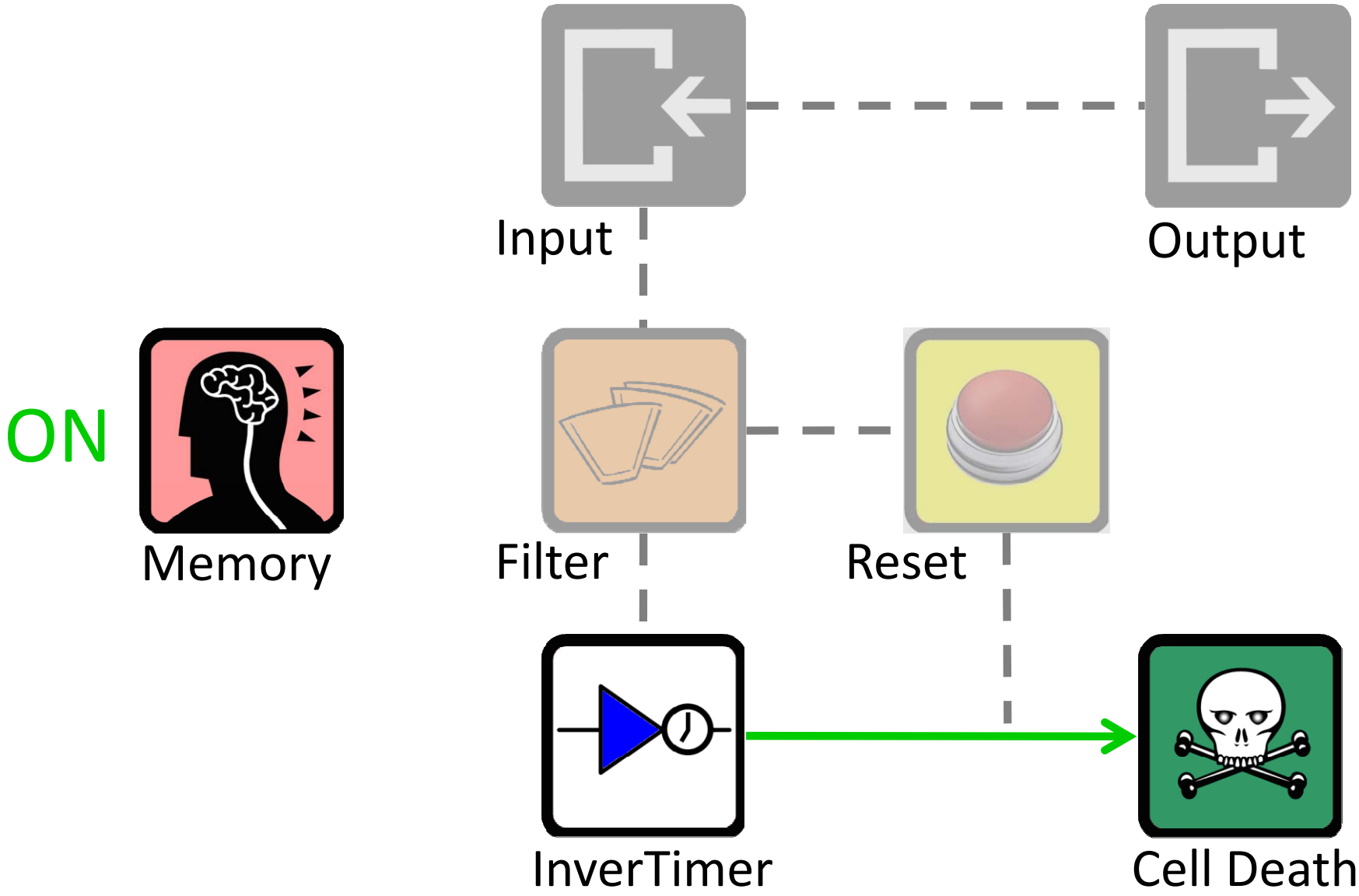
@ work 3: Temp/locally Cured



@ work 4: Patient Relapse

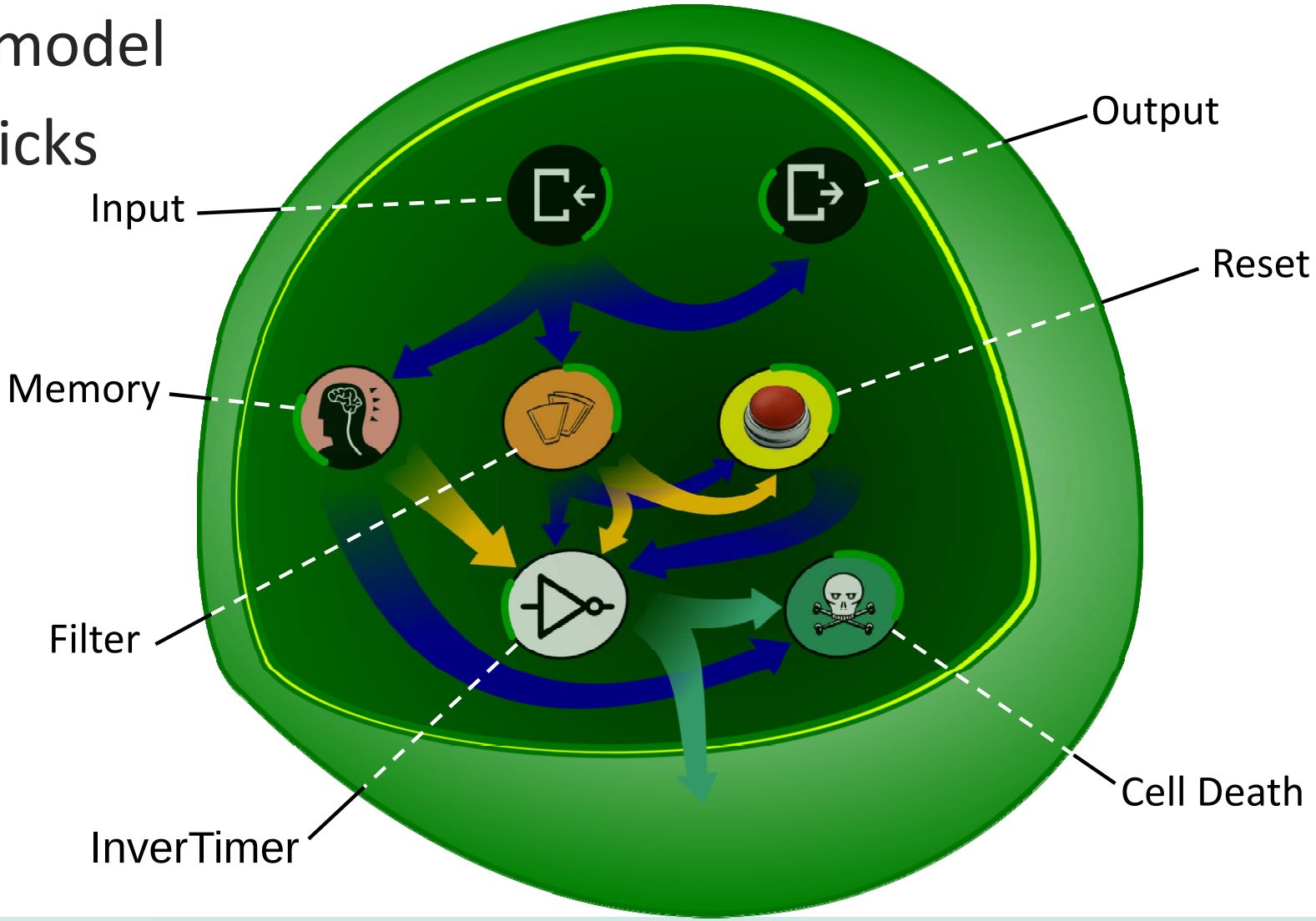


@ work 5: Patient Cured

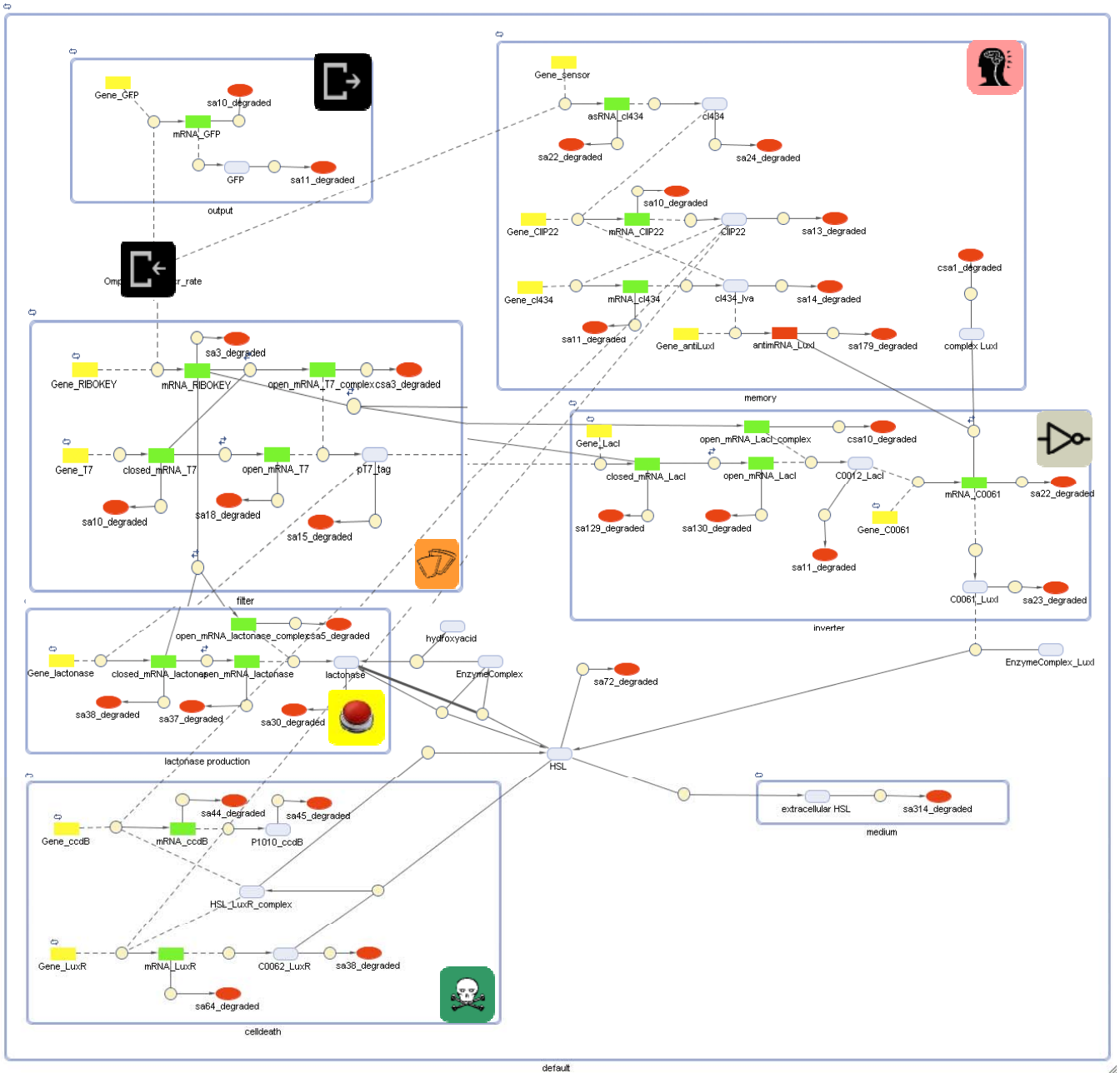


Building Dr. Coli

- from subsystems to integrative model
- reuse BioBricks

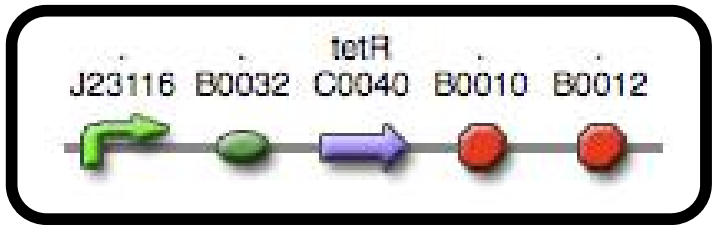


Dr. Coli subsystems



Input - Output

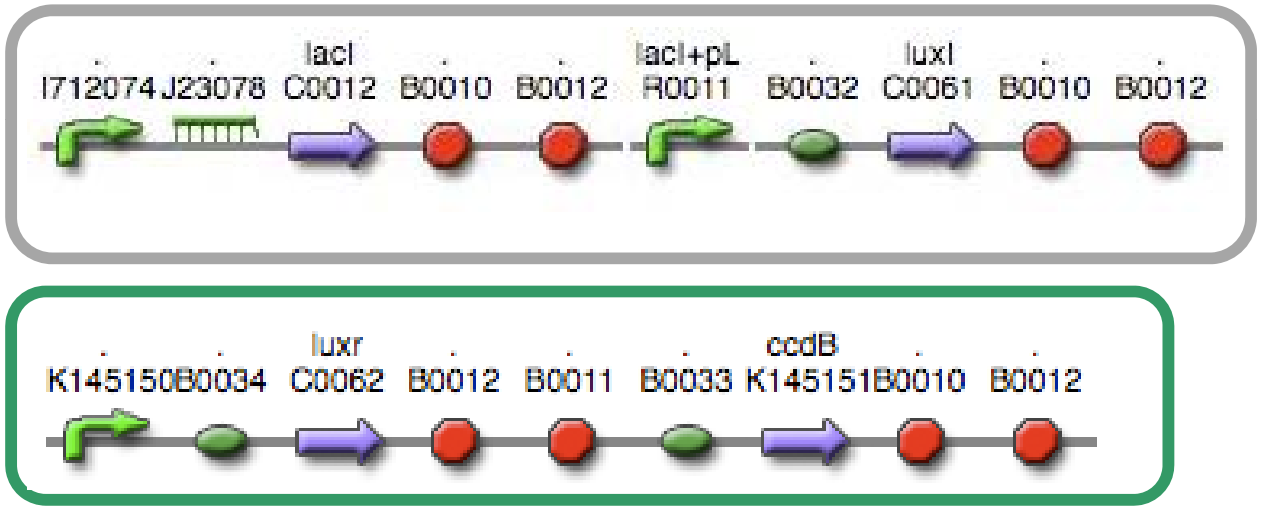
- Input = disease marker
  - Dummy input: TetR ~ aTc



- Output = drug
  - Dummy output: GFP-LVA
    Andersen *et al.* 1998 Appl Environ Microbiol

InverTimer & Cell Death

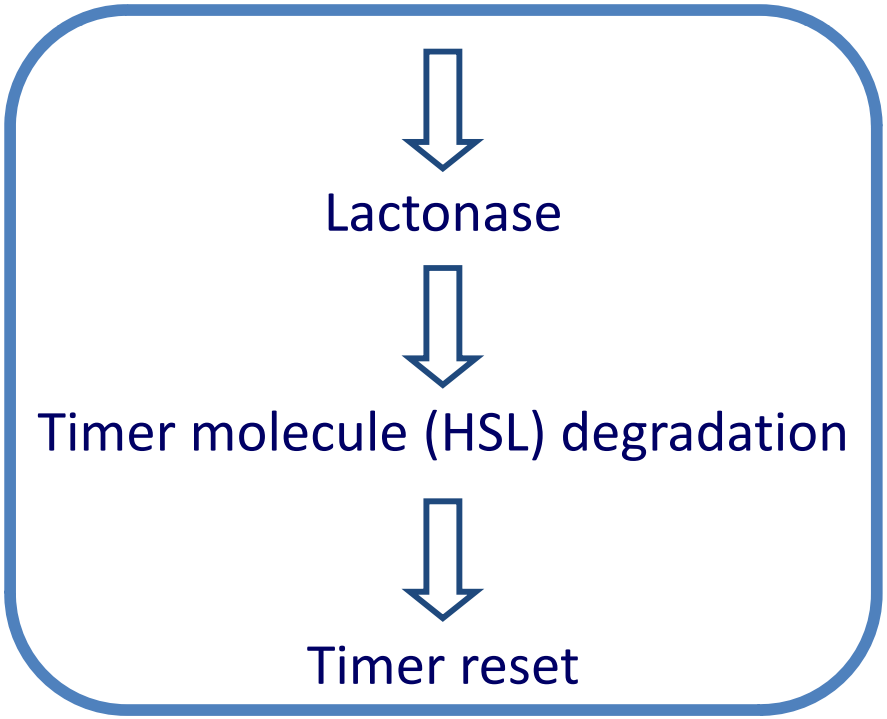
- No disease signal → Dr. Coli dies
  - Inverter
  - Timer molecules (HSL)
  - Suicide gene



Input	InverTimer	Cell death
0	1	1
1	0	0

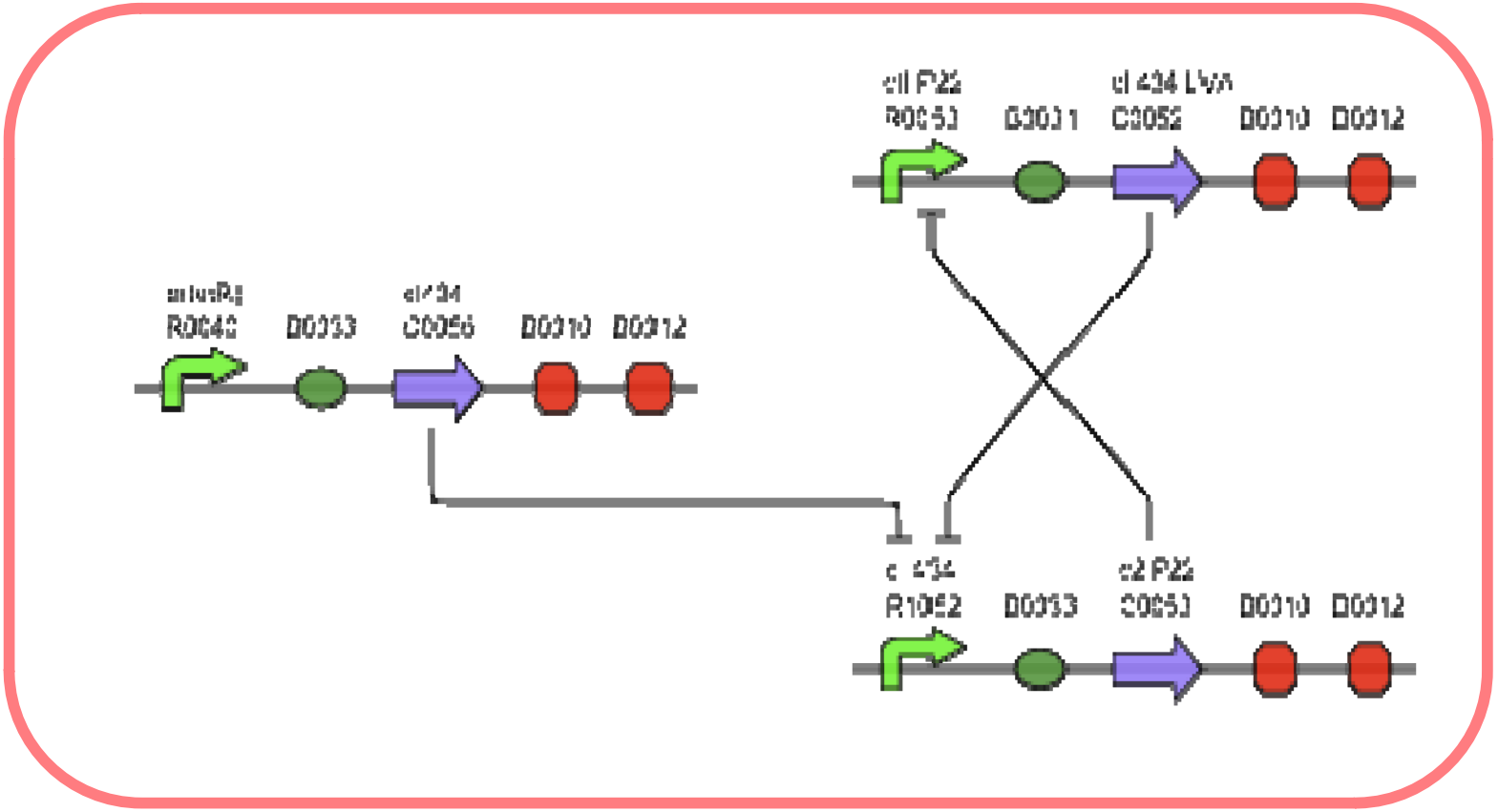
Reset

- Renewed disease signal
- → timer reset

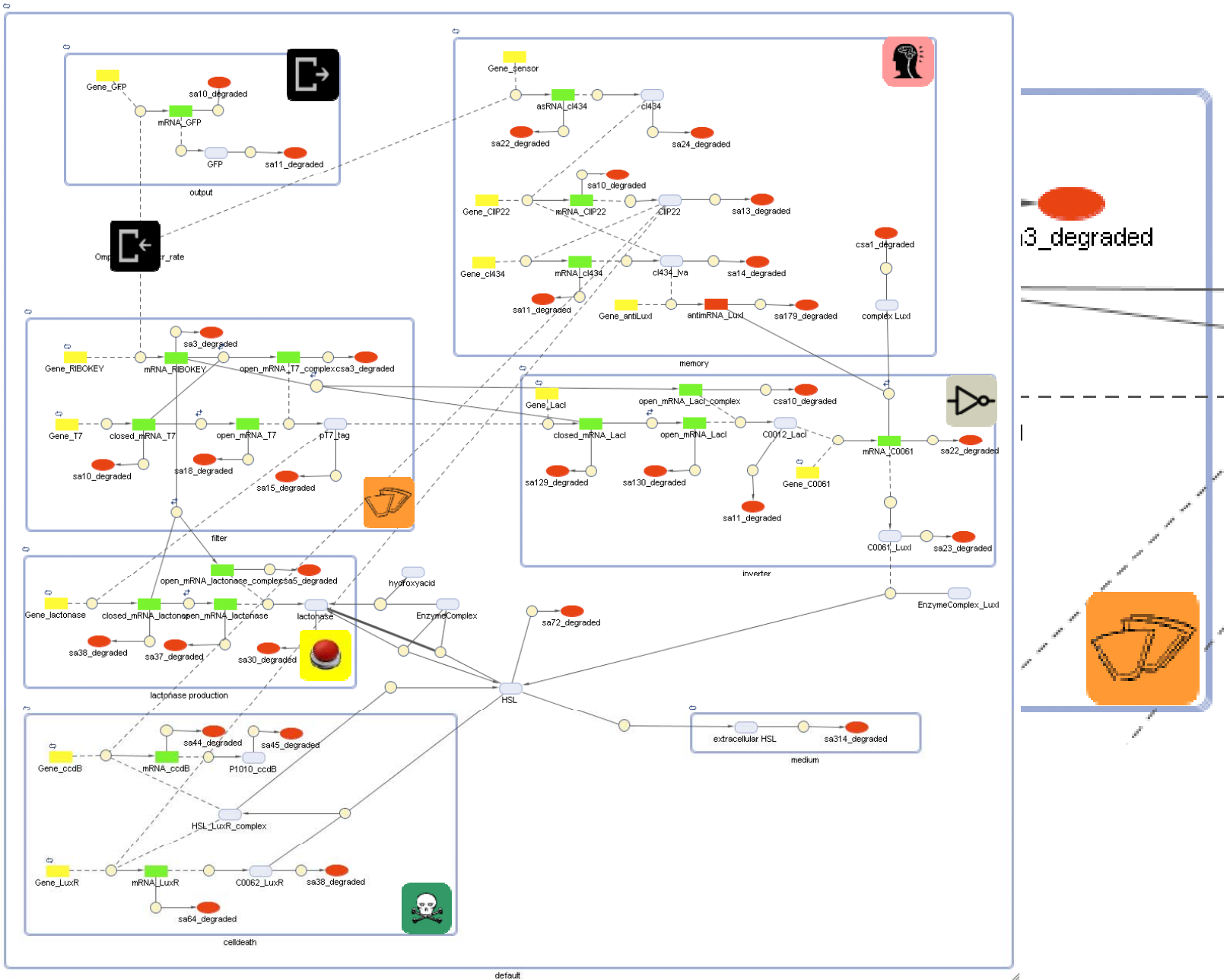


Memory

- Production problem
- One time « ON » switch



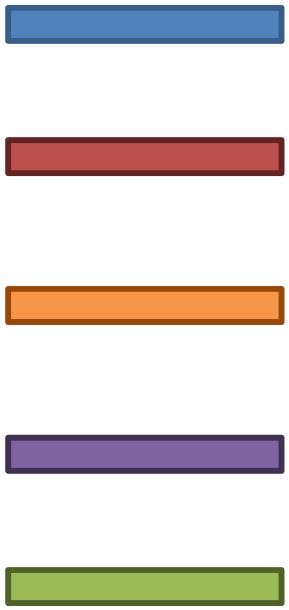
Dr. Coli integrated model



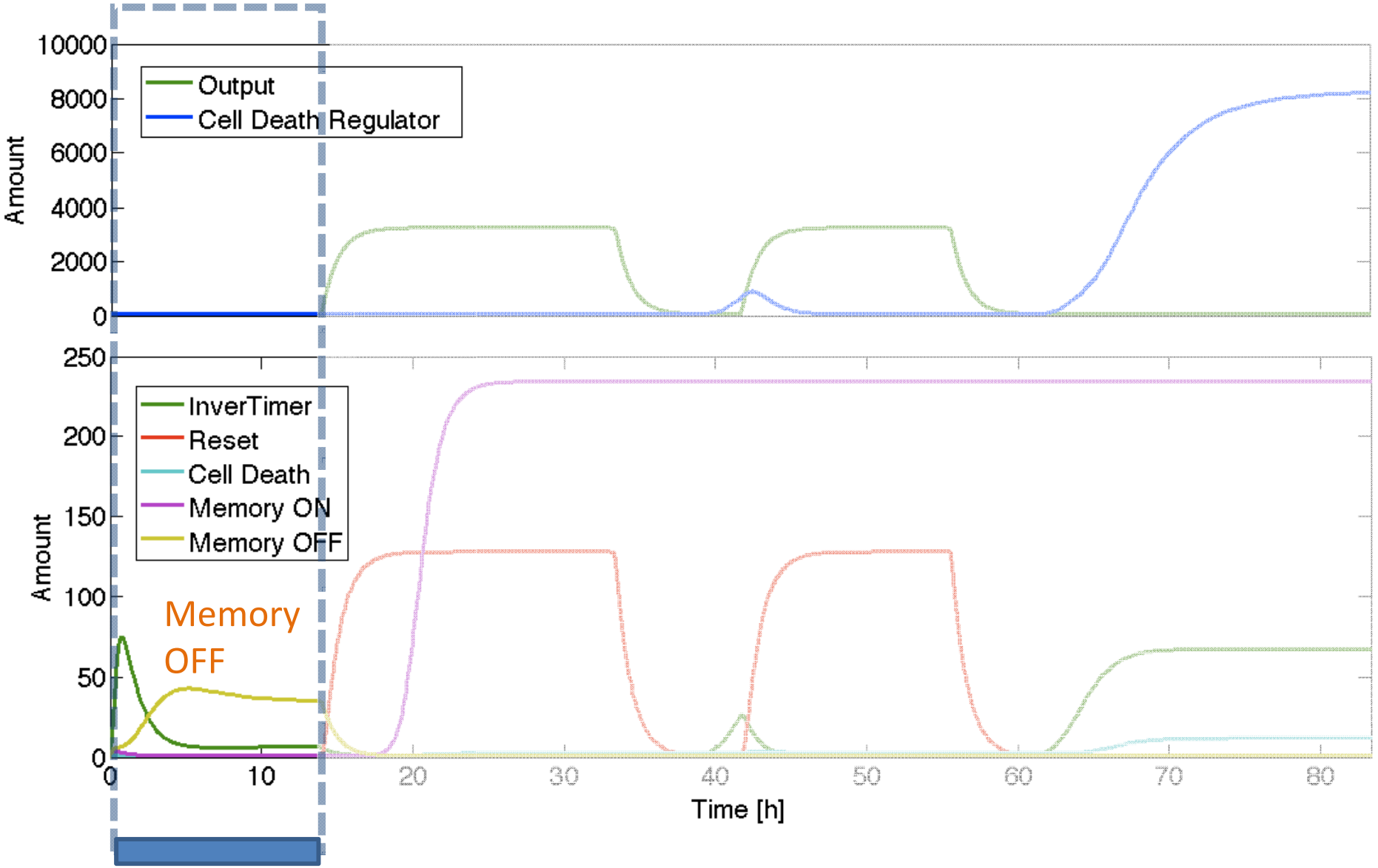
Dr. Coli @ work

Five different phases:

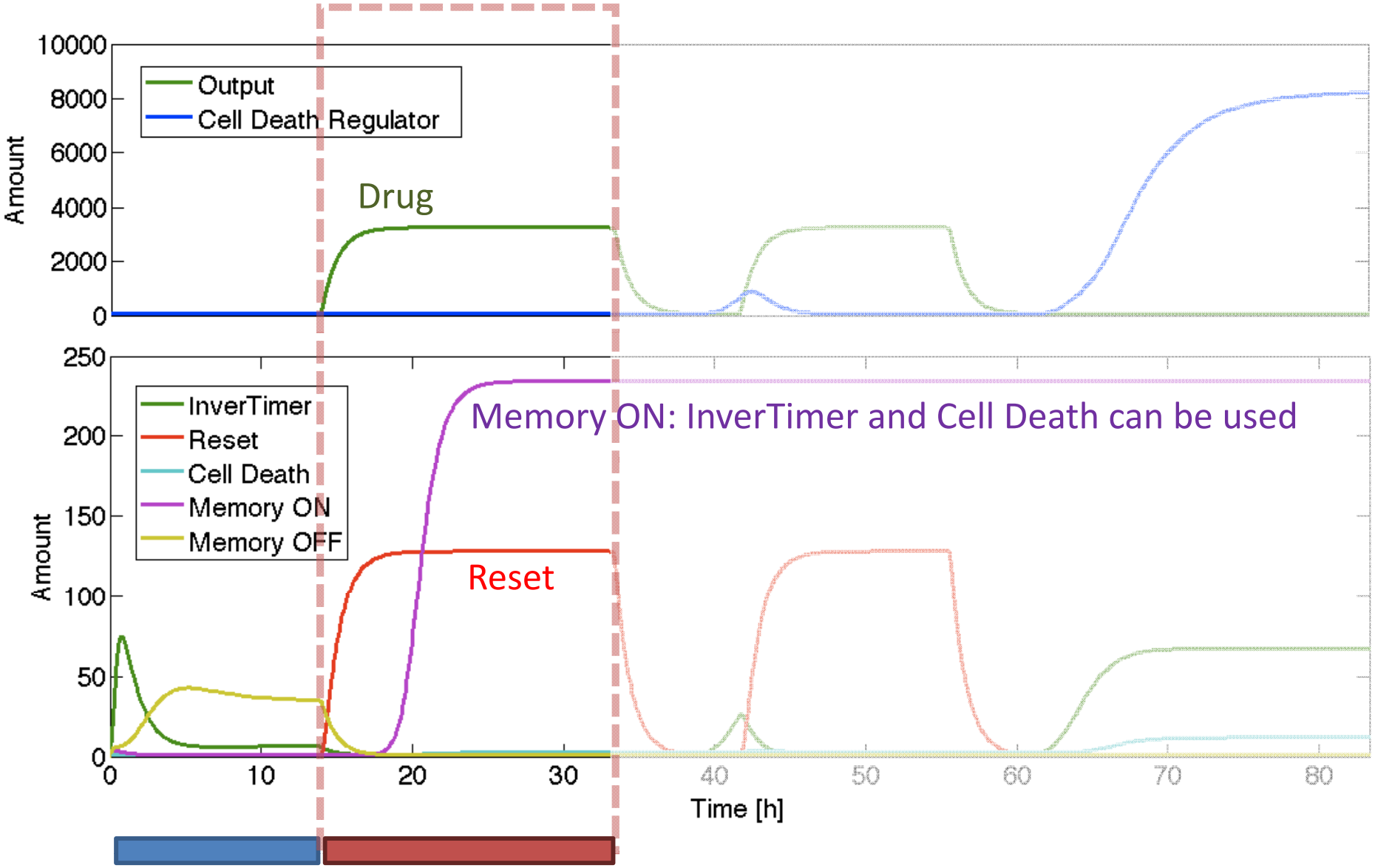
1. No disease signal
2. First disease signal
3. Temporarily/locally cured
4. Patient relapse
5. Patient cured



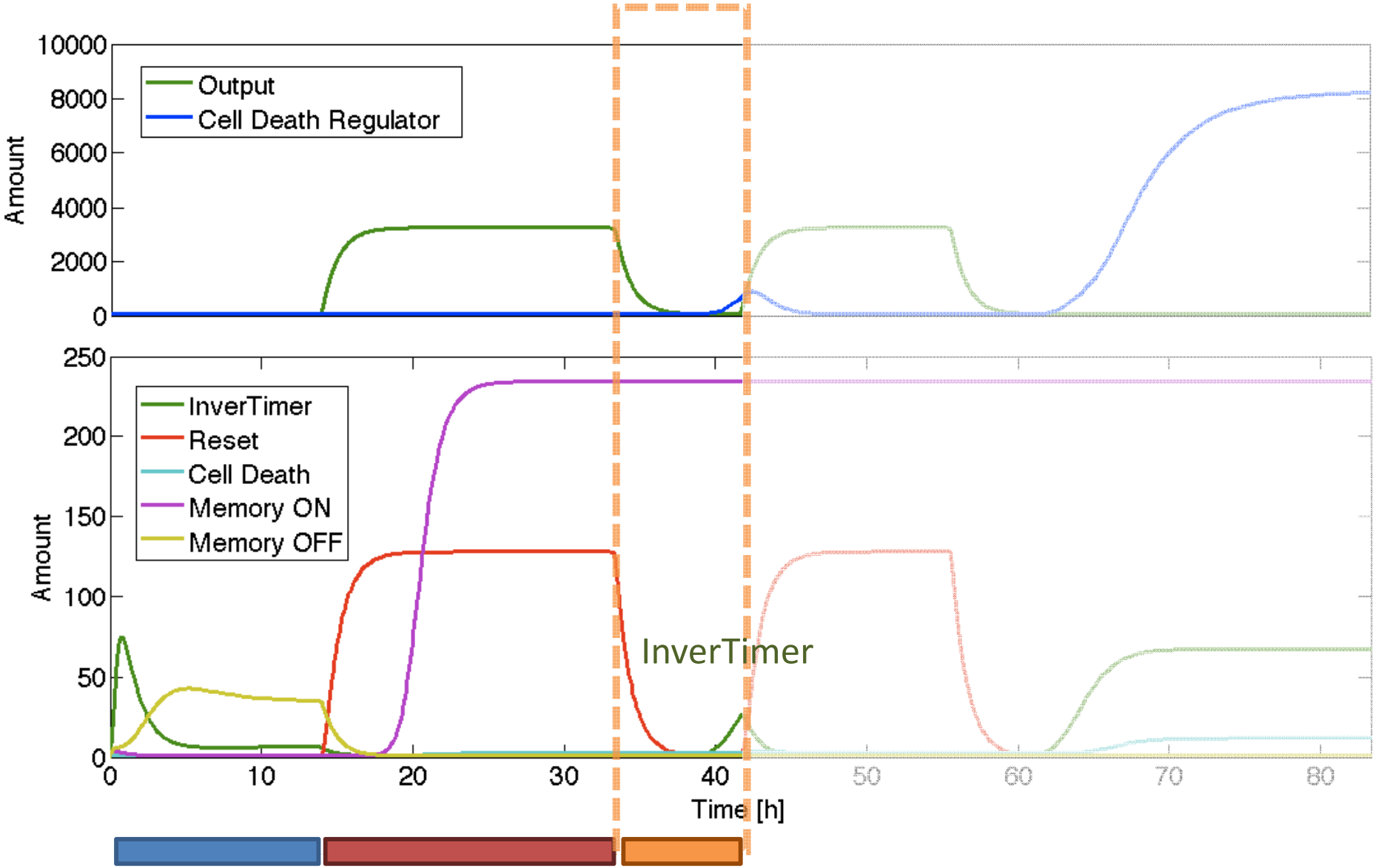
Simulation 1: No Disease Signal



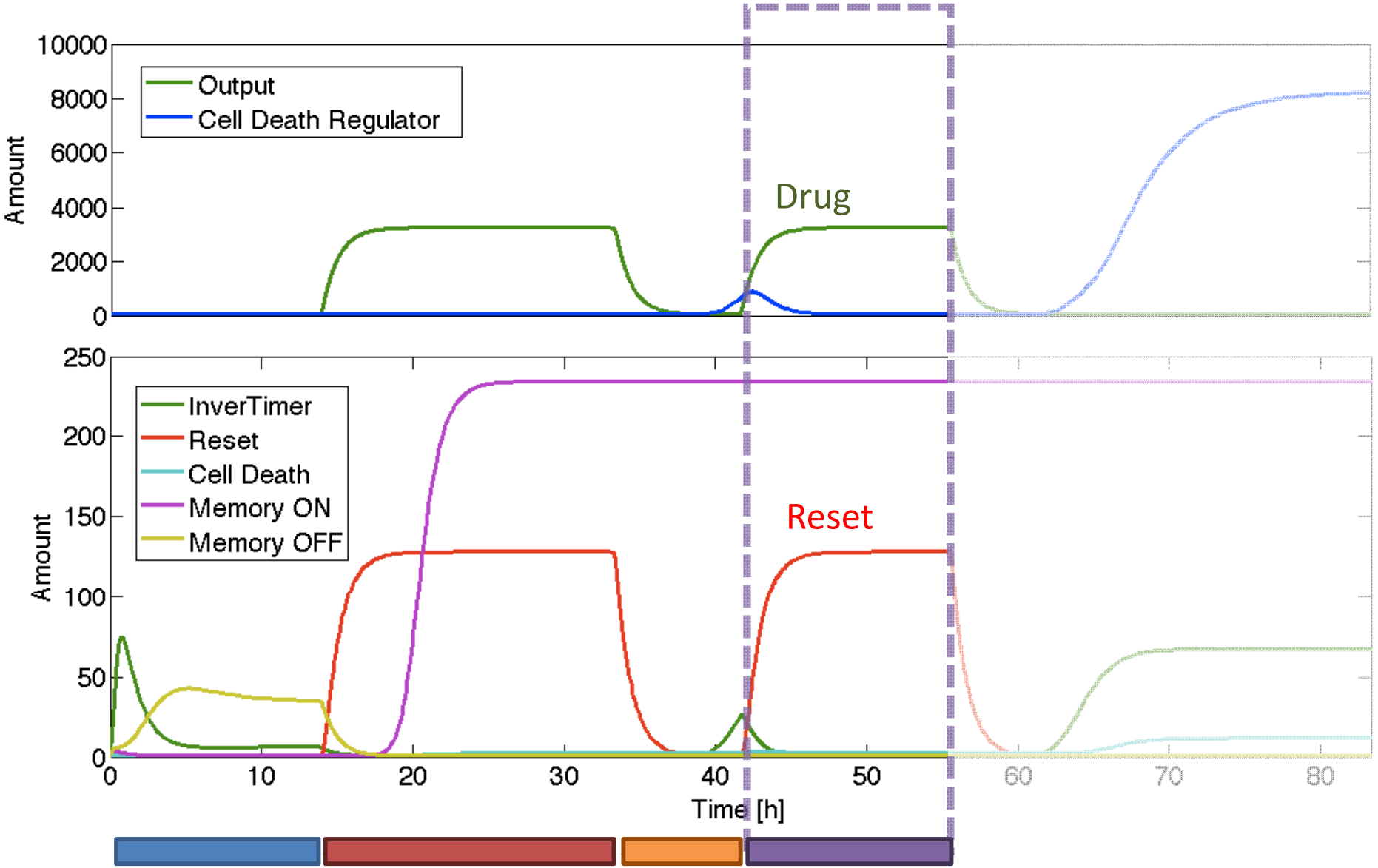
Simulation 2: 1st Disease Signal



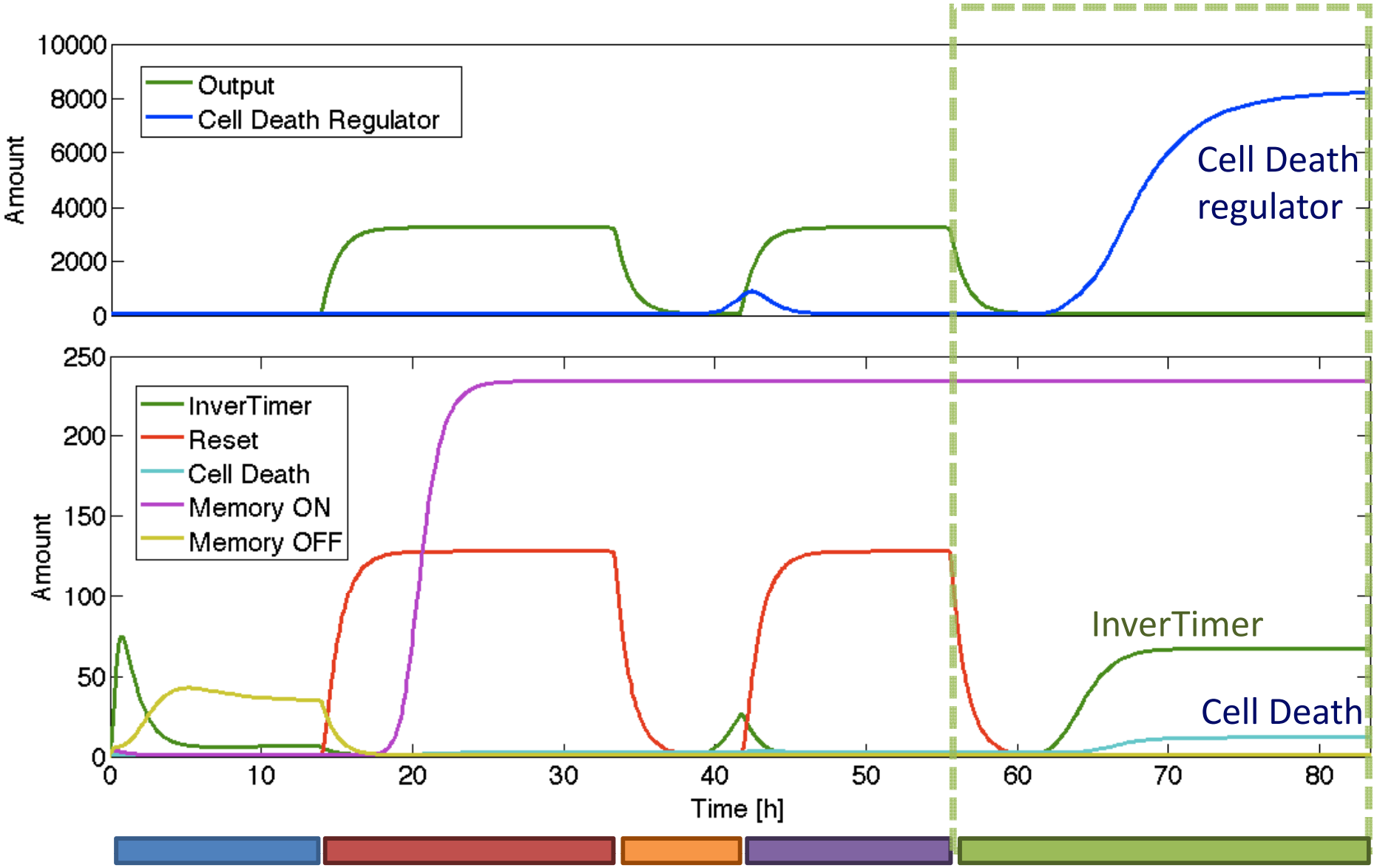
Simulation 3: Temp/locally Cured



Simulation 4: Patient Relapse

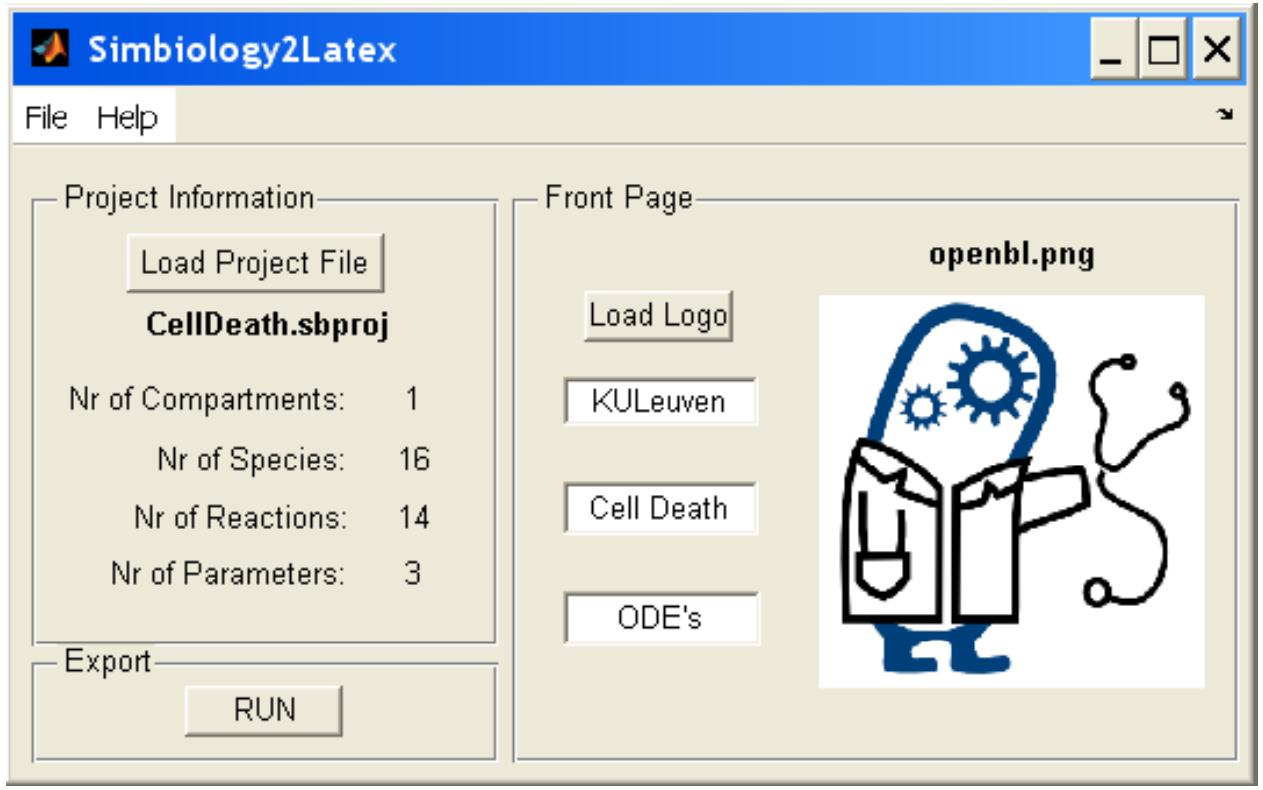


Simulation 5: Patient Cured



SimBiology2LaTeX toolbox

- converts the information in a MATLAB SimBiology model to LaTeX-code (species, parameters and values, reaction rates and ODEs)



Dr. Coli wiki

http://2008.igem.org/Team:KULeuven

2008 iGEM team KULeuven

students: Maarten Breckpot, Nick Van Damme, Benjamien Moeyaert, Dries Vercruysse, Hanne Tytgat, Jan Mertens, Jonas Demeulemeester, Antoine Vandermeersch, Stefanie Roberfroid, Andim Doldurucu, Elke Van Assche, Nathalie Busschaert

instructors & advisors: Inge Thijs, Sigrid De Keersmaecker, Kathleen Marchal, Bart Nicolaï, Astrid Cappuyns, Jos Vanderleyden, Georges Gielen, Yves Moreau, Liesbeth van Oeffelen, Johan Robben, Joris Winderickx, Bart De Moor, CMPG colleagues

sponsor & lab space:
BioSCENTer
Centre of Microbial and Plant Genetics

http://2008.igem.org/Team:KULeuven
www.kuleuven.be/BioSCENTer
www.cmpg.be

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