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Decisions Under Uncertainty in Sygenta

The Role of Inverse Problems and Optimisation in Uncertainty Quantification
Wednesday 17th - Thursday 18th June 2015, ICMS Edinburgh

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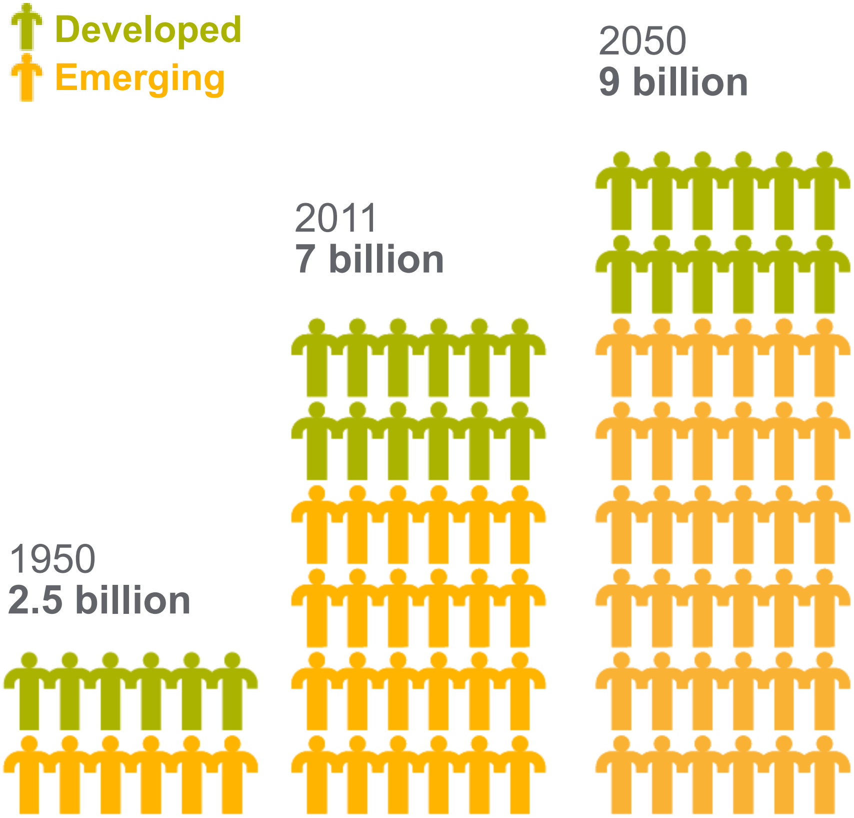
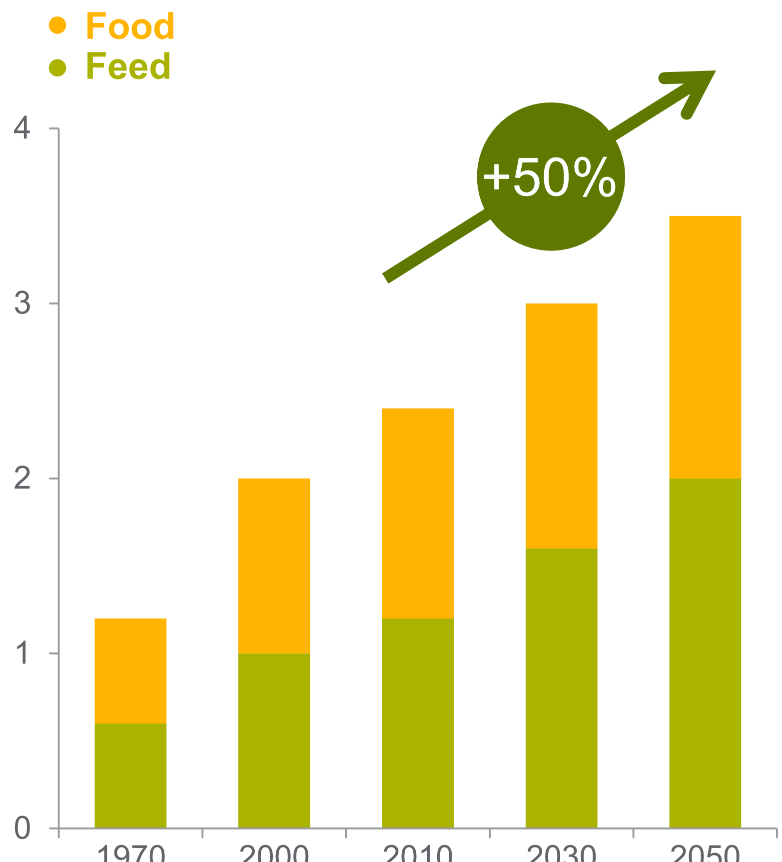
- Food Production
- Syngenta
- The Research Process: Compound Optimization Challenges
- The Development Process: Risk Assessment Challenges
- GIS & Other Challenges
- Summary

Demand for food is driven by population growth and rising calorie consumption

World population
> 80% of growth happens in emerging markets



World demand for major crops*
bn tonnes



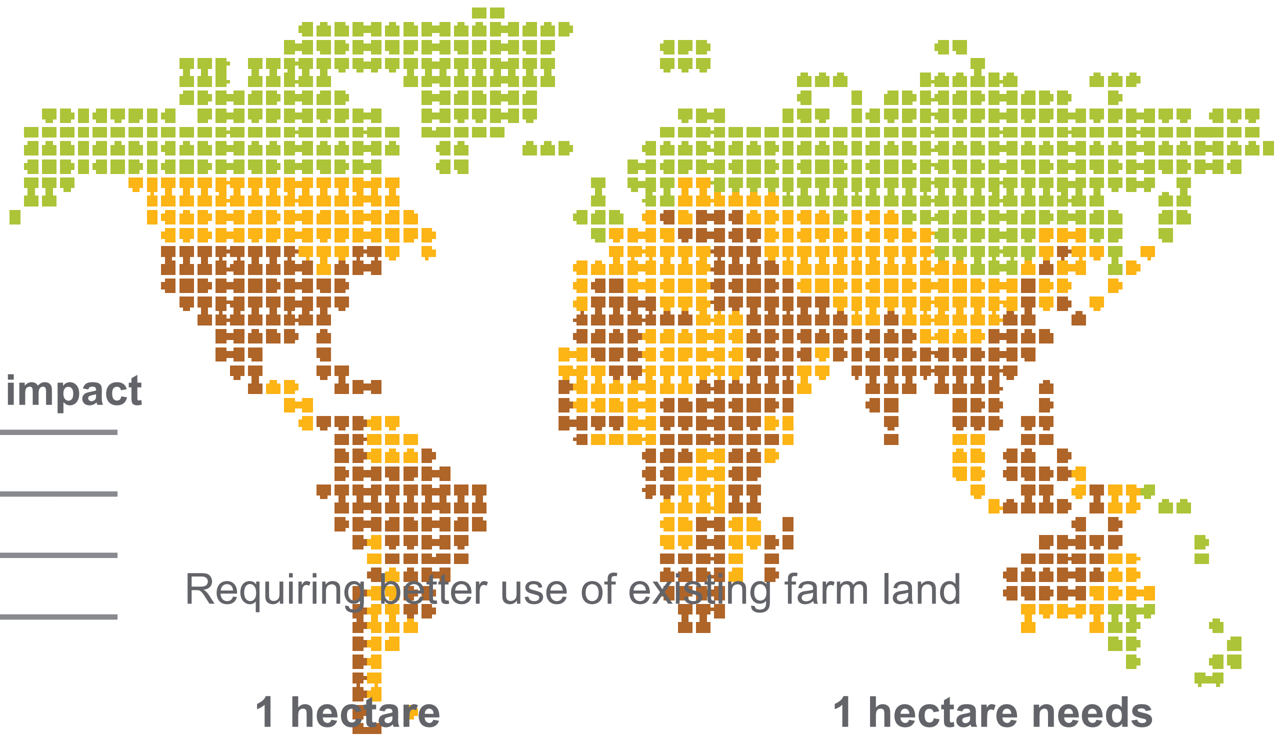
* Includes cereals, rice, corn and soybean

Source: FAO, Syngenta analysis

Environmental stresses are increasing

World stress map

The change in climate is already reducing water and arable land



Climate change impact

- High
- Medium
- Low

Requiring better use of existing farm land

1 hectare fed 2 people — 1950

1 hectare needs to feed 5 people — 2030

Source: UNEP, Cline, Syngenta

Syngenta: passionate people and a strong platform

Over
$1.25 billion
annual R&D investment
and more than
5,000
R&D staff

Over
27,000
employees
in some 90
countries

$14.2bn
sales in 2012

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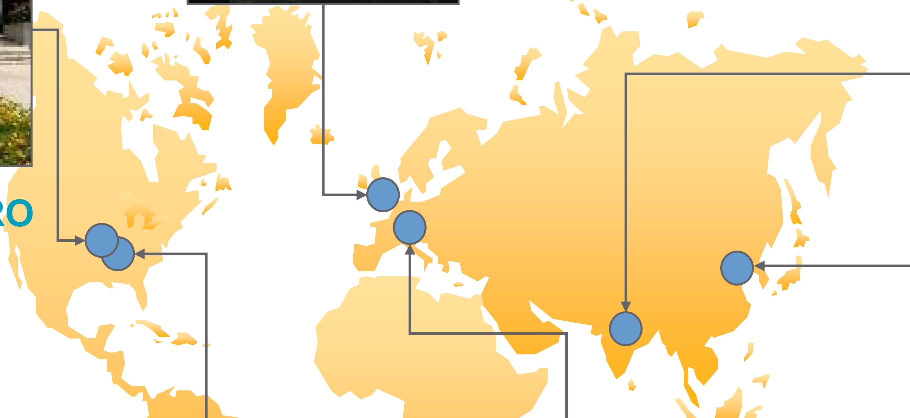
Global R&D capabilities

GOA
Chemistry

JEALOTT'S HILL
Chemical Discovery
Herbicides
Formulation
Product Safety

Major R&D sites
located on three continents

GREENSBORO
Formulation
Product Safety



BEIJING
Biotechnology

RTP
Biotechnology

STEIN
Fungicides, Insecticides &
Professional Products

Other sites

- Marker-assisted and seed breeding capabilities
- Global field station network

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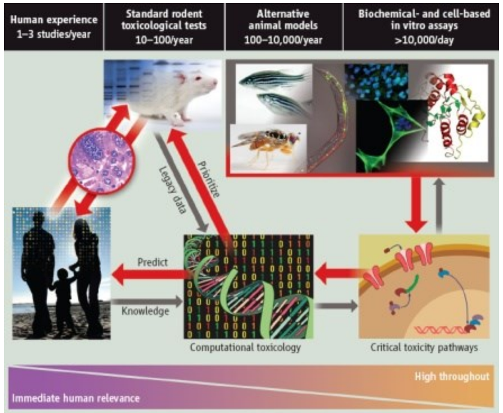
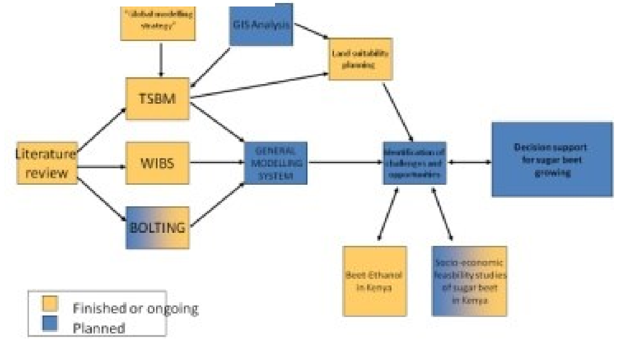
Modelling in Syngenta

Predictive Modelling Network



US-EPA ToxCast initiative

- AI-target molecular
- Predictive toxicology



Sugar beet modelling overview

- Genotype to phenotype prediction
- Systems biology

Biology

- Efficacy
- Crop quality
- Business case
- Crop economics
- Supply chain
- Experimental design

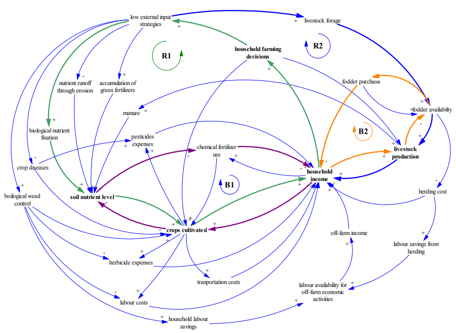
- Crop development
- Pests / weeds / diseases
- Ecosystems

Chemistry

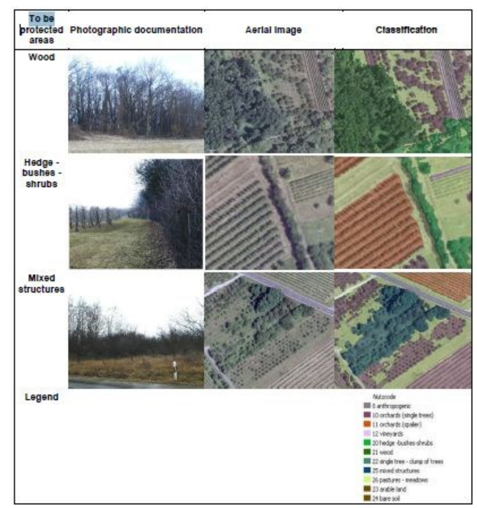
- Computational chemistry
- Formulation
- Chemical production

Environment

- Water
- Soil
- Climate change
- Environmental fate



Low Input Small-Scale Farming System



Geographic information systems, image analysis and ecosystems

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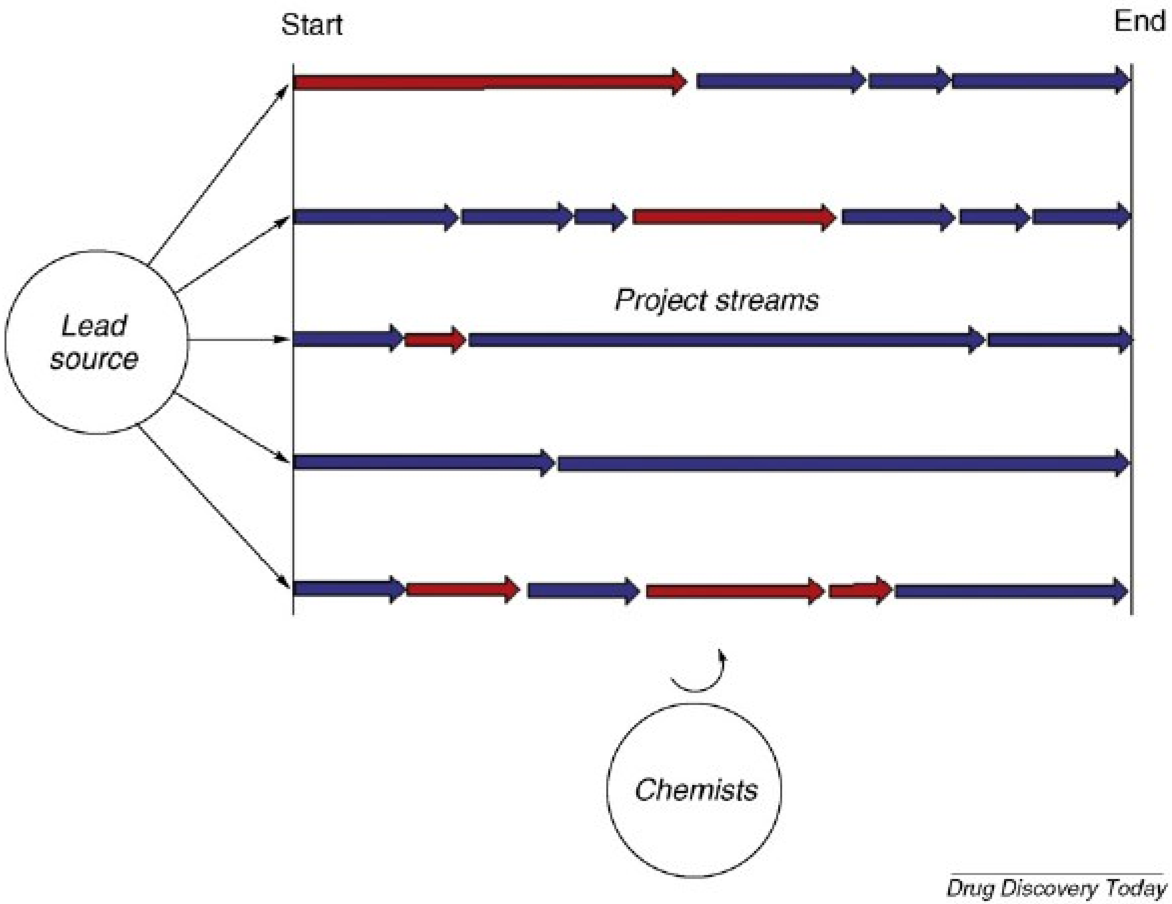
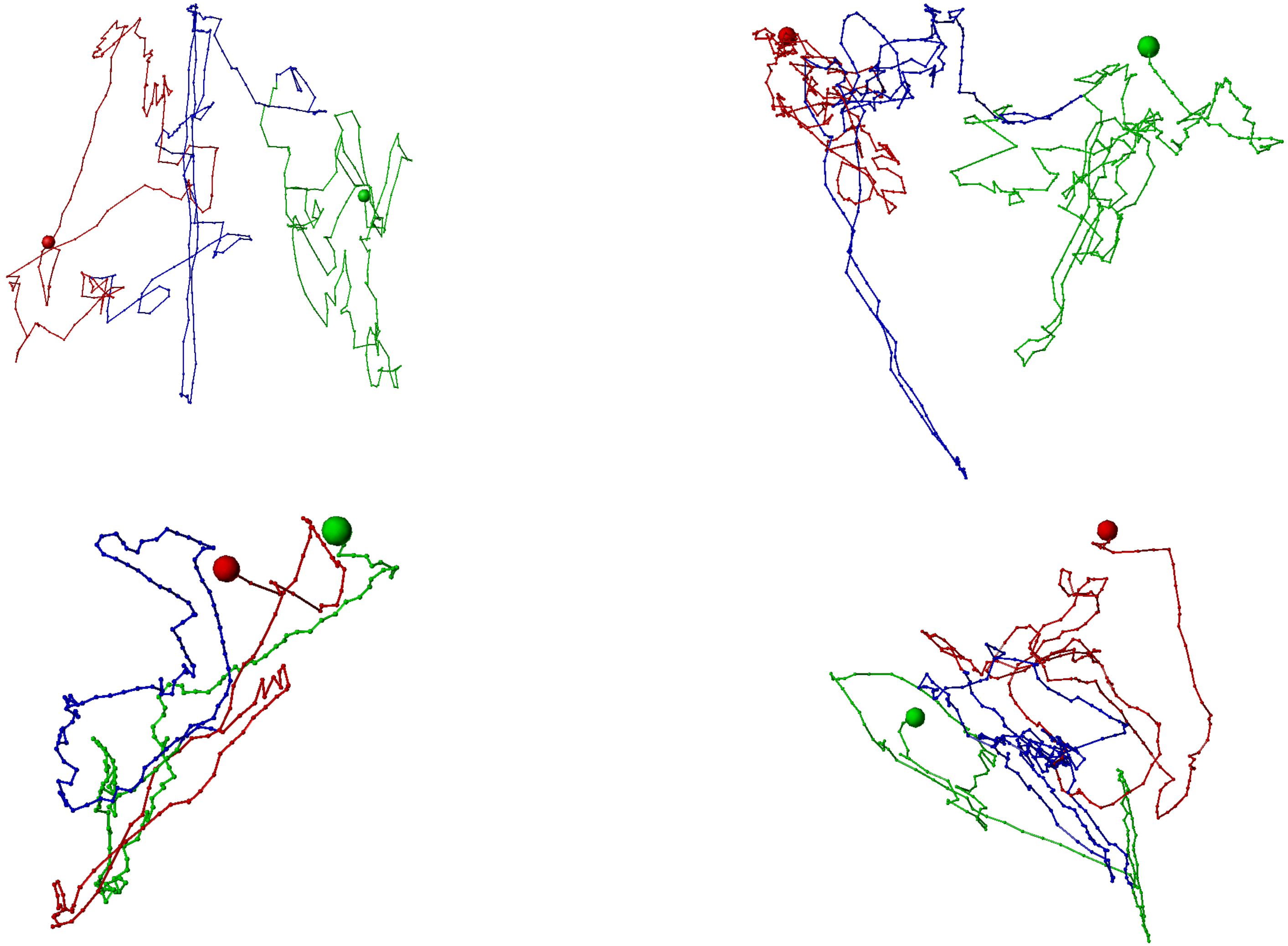
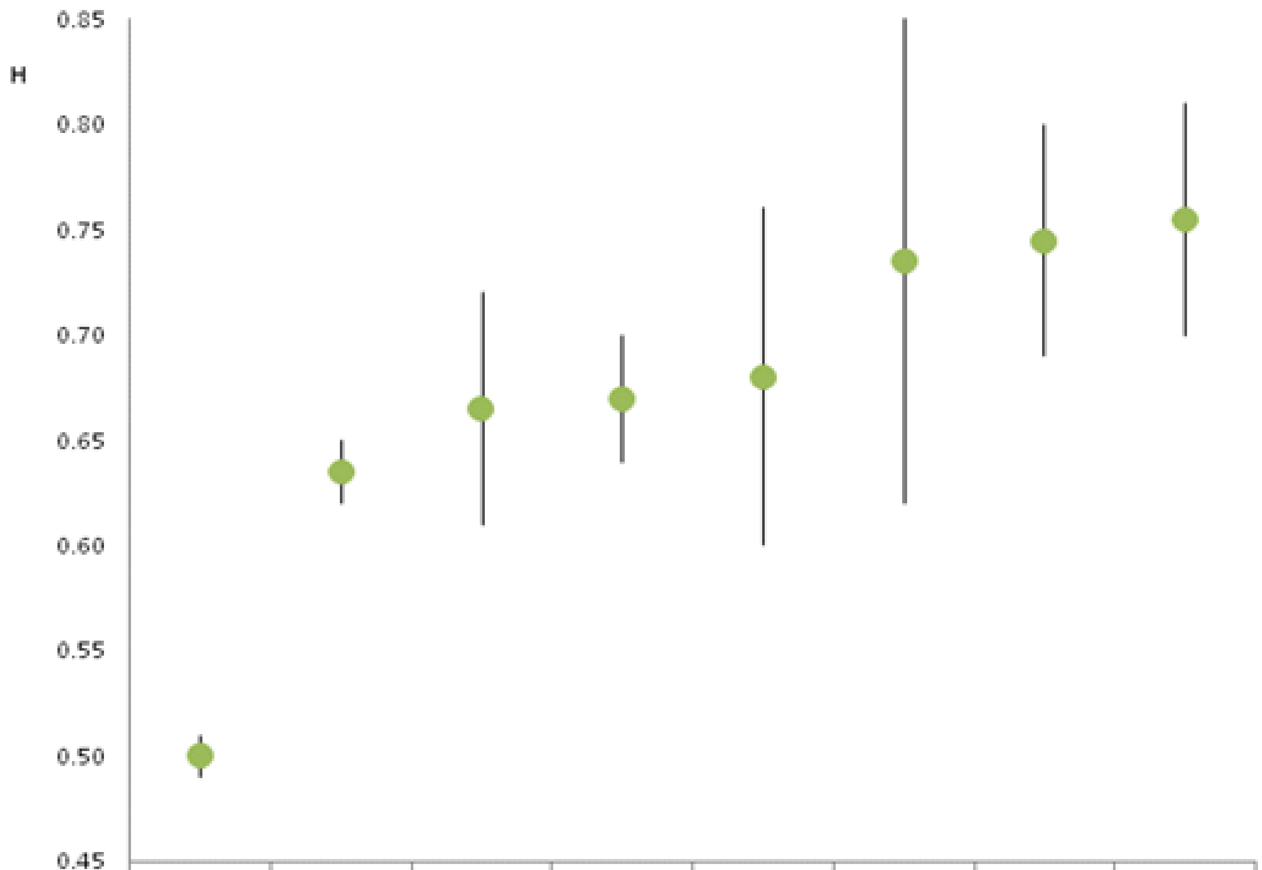
Chemical R&D


Start
End
Lead source
Project streams
Chemists
Drug Discovery Today

Compound optimisation as a random walk



Whittle Estimates for H



	20kRW	20kSARW	H1 (528)	H2 (893)	F1 (308)	H3 (225)	H4 (584)	Axial (695)
Lower	0.49	0.62	0.61	0.64	0.60	0.62	0.69	0.70
Upper	0.51	0.65	0.72	0.70	0.76	0.85	0.80	0.81
Mean	0.50	0.64	0.67	0.67	0.68	0.74	0.75	0.76

Ref: John Delaney. Modelling iterative compound optimisation using a self-avoiding walk. Drug Discovery, volume 14, 2009.

Activity cliffs

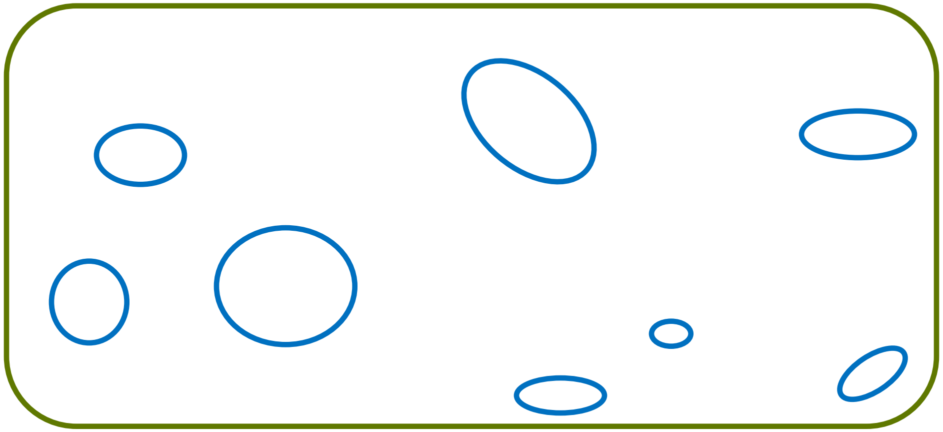
But sometimes parts of chemical space look like this

Normally models assume that chemical space looks like this

or this

Global vs Local QSARs

Chemical Space



 = individual projects

We can fairly easily do global QSARs (across whole chemical space)

We really want local QSARs (a QSAR for each project) but we rarely have enough data until it is no longer useful

Potential Proposal

Develop a hybrid global/local approach

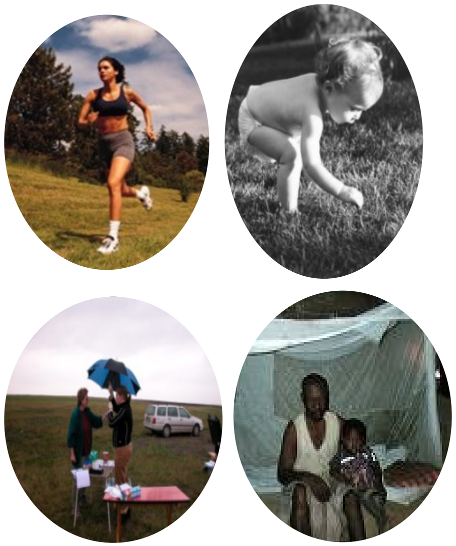
- e.g. use physicochemical parameters globally, and structural fragments locally

Very limited precedent in chemoinformatics QSAR literature, but doable

NON-DIETARY EXPOSURE ASSESSMENT SCENARIOS

Operators

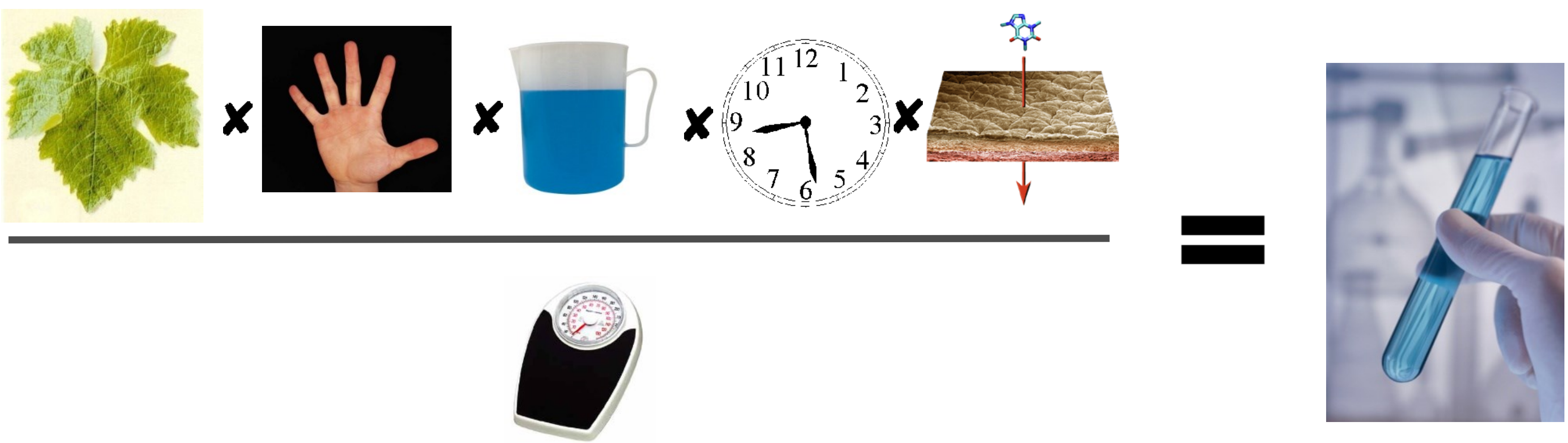
Residential & Bystanders



Worker Re-Entry

Risk Assessment: Worker Re-Entry

(DFR x TC x AR x H x DA) / BW = predicted exposure

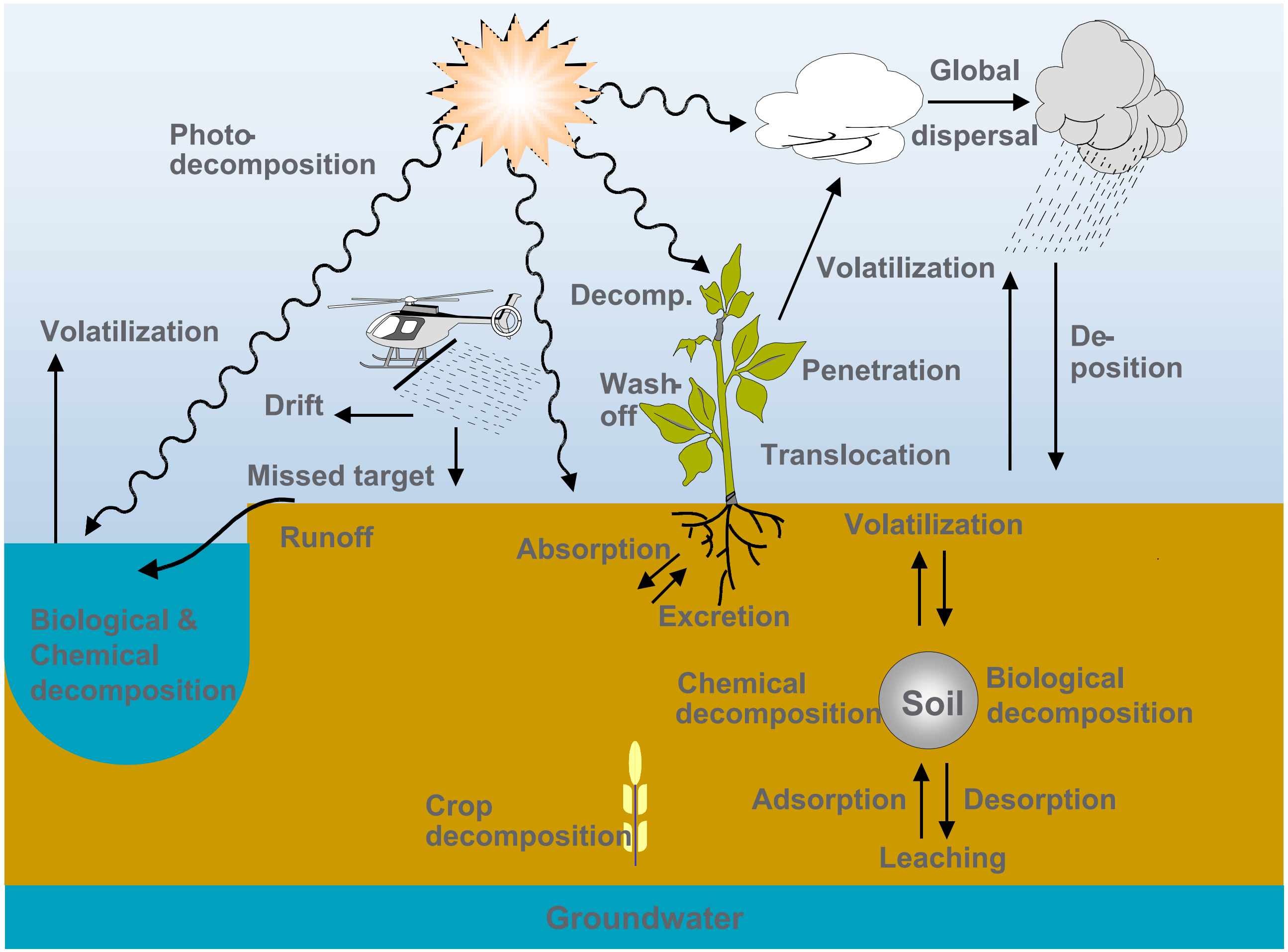


Risk Assessment: a Multi-Objective Multi-Level Optimization Problem under Uncertainty

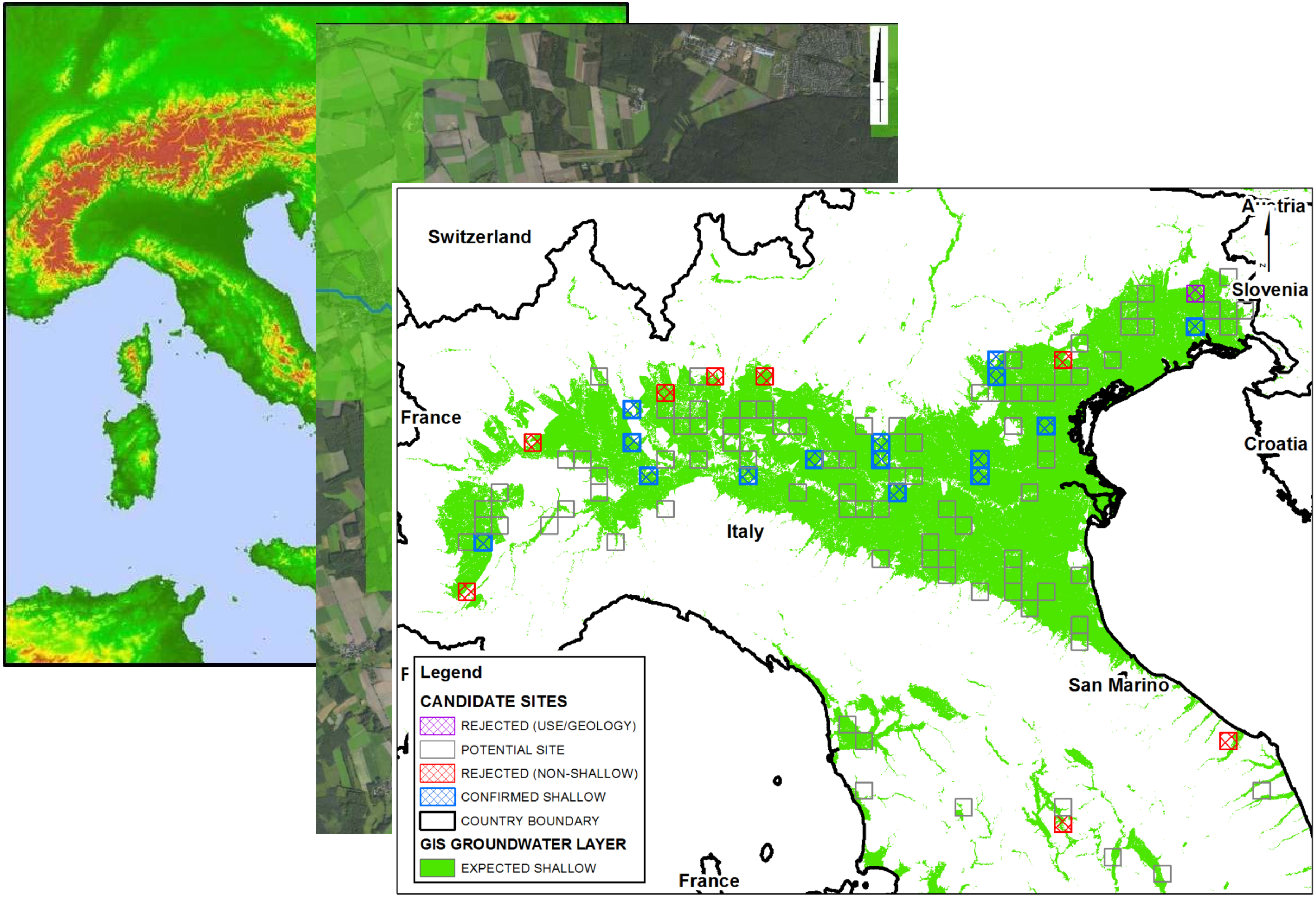
- We would like to stay as close as possible to the optimal parameter use values based on efficacy considerations → **optimization problem!**
- Ideally we would like to make each risk estimate as low as possible due to risk cup considerations and new EU regulations on compound selection → **multi-level optimization problem!**
- We need to pass a number of risk assessments in the consumer, operator, ecological and environmental areas → **many constraints!**
- Changes in some of the parameters involves in the risk assessments can make the passing of one assessment easier at the expense of making another one more difficult (e.g. droplet size, leaf wash off).
  - We need to construct **Pareto fronts** in order to make decisions.
- We have to take safety decisions early in the development process → **decisions under uncertainty.**
- We also need to decide whether optional studies will be needed or even if they would be helpful (e.g. DFR studies).

The Development Process: Risk Assessment & Monitoring

Quantities in soil, water or air: persistence & movement



- Laboratory Studies
  - Fate Processes
- Field Studies
  - Actual residue
  - Movement
- Simulation Modelling
  - Prediction
  - Sensitivity



Ref: Poster by Timothy Negley, Andrew Newcombe (ARCADIS);
Paul Sweeney, Lucy Fish (Syngenta Ltd.); and Paul Hendley (Phasera Ltd.)

Other Challenges (Inverse Problems)

- We measure the properties of candidate formulations, eg cloudiness, crystallisation and seek to infer the hidden variables causing these undesirable properties.
- We measure the acute toxicity of many of our formulations   We now like to infer the acute toxicities of all formulation ingredients (not just AIs) from the accumulated historical dataset.
- We manufacture AIs and over months and years tweak the processes to improve efficiency / reduce cost or waste / improve purity / control specific impurities.
- The big prize would be to use inverse modelling to look at:
  - Field trials / fields where we do and don’t see efficacy
  - Fields where we do and don’t see resistance
  - Fields where we do and don’t see carryover

  And infer the underlying driving variables

Summary

- We are facing a "perfect storm" situation in food production.
- At Syngenta, we have many challenges relating to making decisions under uncertainty during the research, development and manufacturing of our agrochemicals and seeds.
- Any ideas or even expressions of interest are very welcomed!

Thank you!