



UCL
Université
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de Louvain

AGRO
LOUVAIN

LBRAI2219 - 2017/2018

MODÉLISATION DES SYSTÈMES BIOLOGIQUES

X. DRAYE & G. LOBET

LBRAI2219 - 2017/2018

1. INTRODUCTION

X. DRAYE & G. LOBET

THÈMES ABORDÉS

- ▶ Introduction à **biologie des systèmes**
- ▶ Introduction aux notions de **réseaux** dynamiques et compartimentés
- ▶ **Formalismes mathématiques** et outils logiciels pour l'exploration des données de type omics
- ▶ Initiation à la **modélisation** (exercices pratiques)

ACQUIS D'APPRENTISSAGES

- ▶ Connaître et comprendre un socle de savoirs approfondis dans le domaine de l'analyse et de la gestion de l'information en ingénierie biologique (M1.1, M1.2, M2.2)
- ▶ Maîtriser des outils spécialisés en Sciences de l'ingénieur ' analyse des systèmes et modélisation (M2.3)
- ▶ Résumer un état des connaissances (M3.1)
- ▶ Analyser et interpréter les résultats pour une problématique scientifique complexe (M3.6)
- ▶ Faire preuve d'une capacité d'abstraction conceptuelle et de formalisation dans l'analyse et la résolution de problèmes complexes (M4.4)
- ▶ Comprendre et exploiter des articles scientifiques et documents techniques en anglais (M6.1)
- ▶ Elaborer des schémas logiques pour poser une problématique complexe de façon synthétique (M6.3)
- ▶ Communiquer de manière synthétique et critique l'état des connaissances dans un domaine spécifique (M6.4)

CONTENU DU COURS

- ▶ Vue générale de la **biologie des systèmes**
 - ▶ Théorie des systèmes et biologie
 - ▶ Topologie, éléments de graphes et attributs de réseau
 - ▶ Identification des noeuds et cartographie des interactions
 - ▶ Inférence de réseaux
 - ▶ Intégration des données
 - ▶ De la structure à la dynamique
- ▶ 2. **Outils informatiques** pour l'exploration de données (omics)
- ▶ 3. Langages et **études de cas**
 - ▶ L-Systems (structure) et FSPM (structure et fonction)
 - ▶ Interactions organisme - environnement
 - ▶ Etudes de cas à diverses échelles (réseau de gène, cellule, tissu, organe, organisme)

MÉTHODES D'ÉVALUATIONS

- ▶ Présentation d'un ou plusieurs séminaires



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2. BIOLOGIE DES SYSTÈMES

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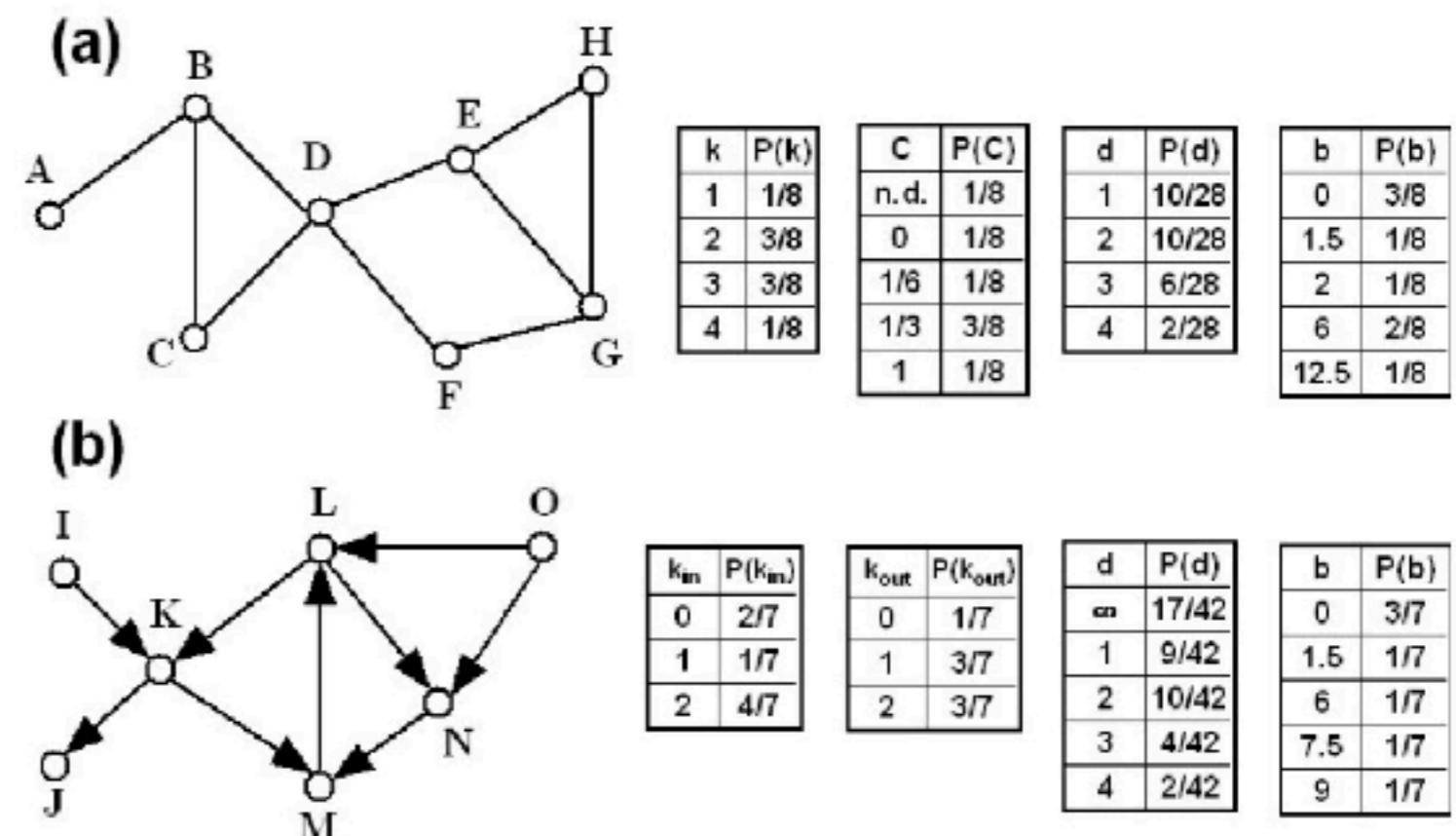
AN OVERVIEW OF SYSTEMS BIOLOGY

- ▶ Lecture d'article
- ▶ Concepts clés:
 - ▶ Systems theory
 - ▶ Graph and network theory
 - ▶ Biological networks

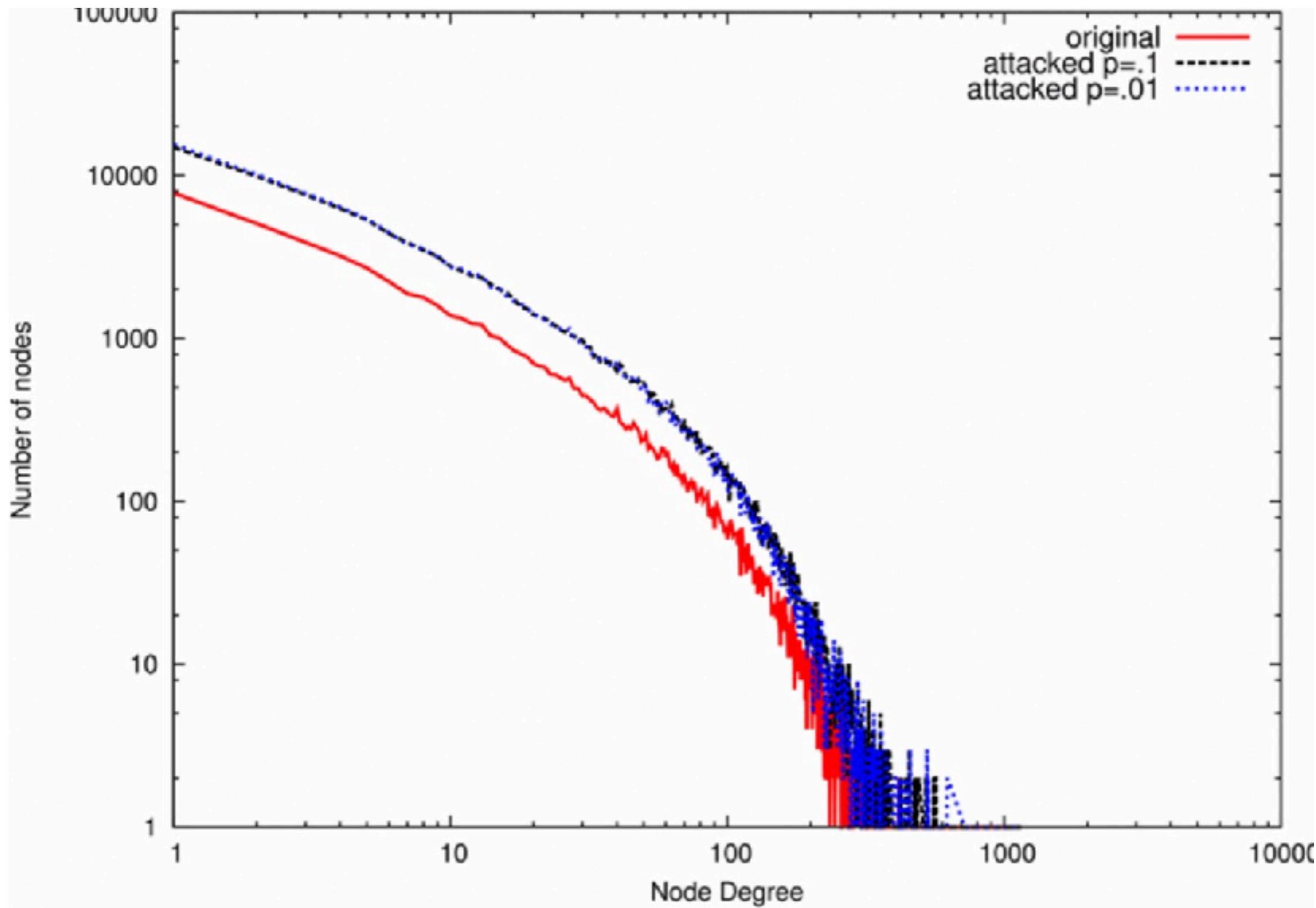
Albert, R. & Assmann, S. M. **An Overview of Systems Biology.** in *Annual Plant Reviews Volume 35: Plant Systems Biology* 41-66 2009

GRAPH ELEMENT AND NETWORK ATTRIBUTES

- ▶ Node
- ▶ Edge
- ▶ Node degree
- ▶ Neighbourhood
- ▶ Clique
- ▶ Clustering coefficient
- ▶ Graph distance
- ▶ Between centrality

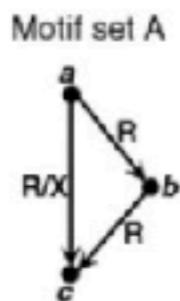


GRAPH ELEMENT AND NETWORK ATTRIBUTES

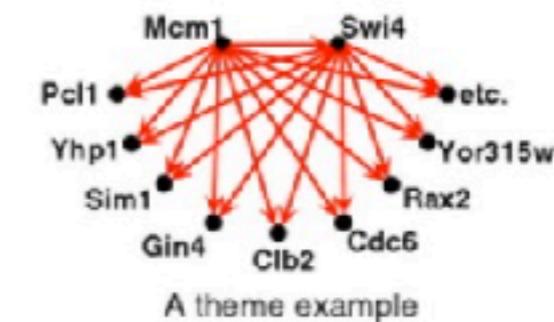
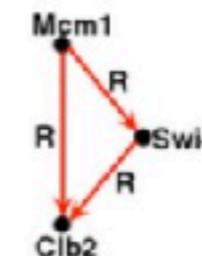


MOTIFS

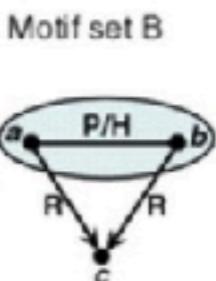
(a)



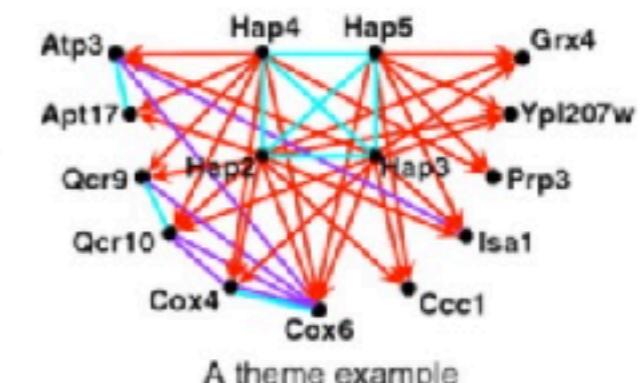
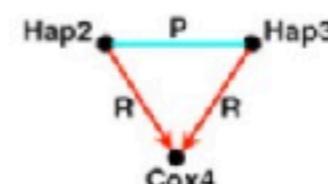
	A1	A2
N_{real}	4.7×10^2	3.0×10^1
N_{rand}	$(2.6 \pm 0.5) \times 10^1$	5.4 ± 3.2



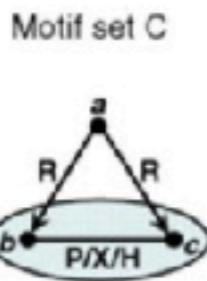
(b)



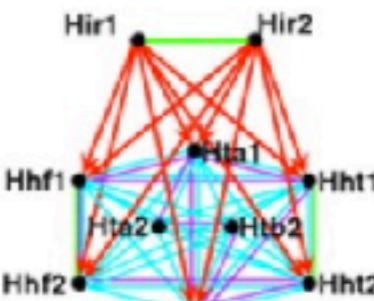
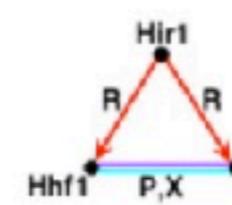
	B1	B2
N_{real}	1.3×10^2	6.1×10^1
N_{rand}	3.3 ± 3.7	$(8.0 \pm 2.3) \times 10^1$



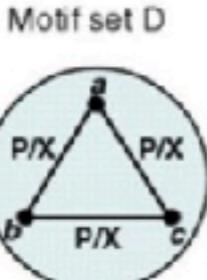
(c)



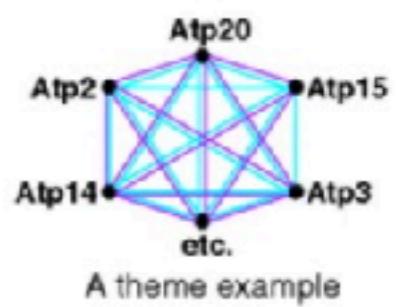
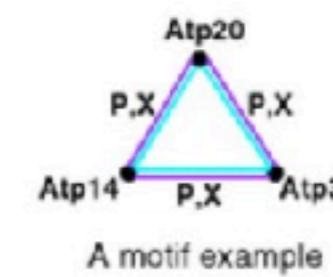
	C1	C2	C3
N_{real}	5.9×10^3	3.5×10^3	1.9×10^3
N_{rand}	$(5.4 \pm 0.5) \times 10^3$	$(2.7 \pm 0.3) \times 10^3$	$(5.3 \pm 0.5) \times 10^3$



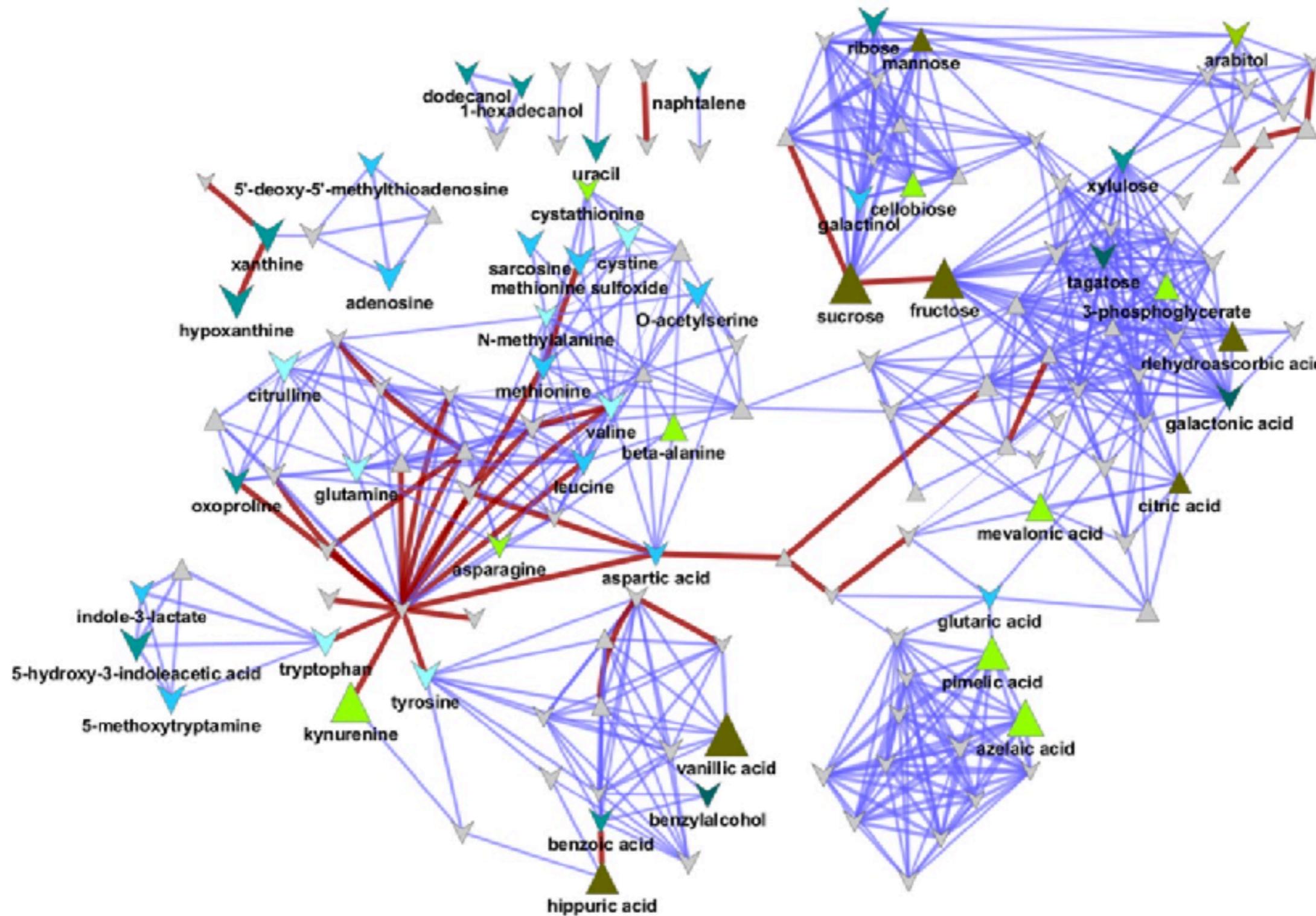
(d)



	D1	D2	D3	D4
N_{real}	5.7×10^5	9.9×10^6	6.7×10^4	1.2×10^6
N_{rand}	$(1.1 \pm 0.0) \times 10^5$	$(8.2 \pm 0.3) \times 10^6$	$(5.2 \pm 0.2) \times 10^3$	$(2.7 \pm 0.1) \times 10^6$



MODULES





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3. MODEL EXAMPLES

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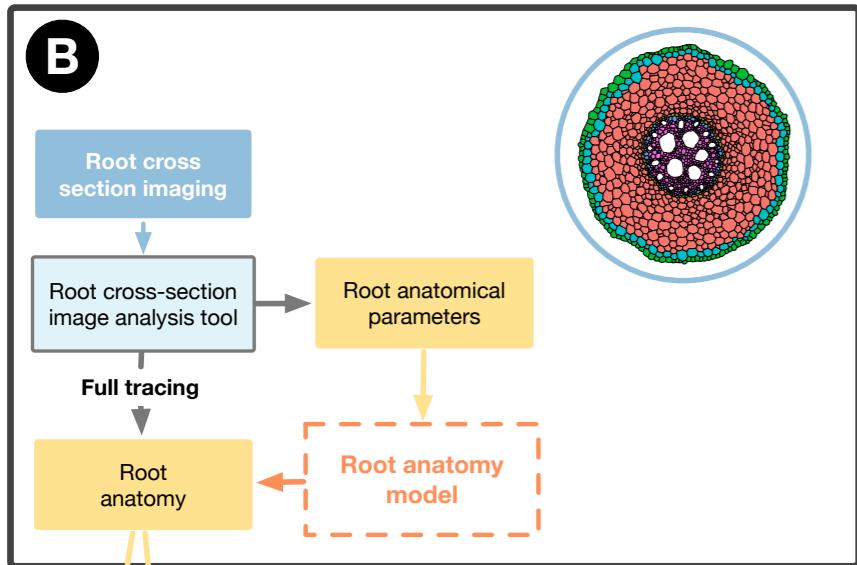
**ALL MODELS ARE WRONG,
BUT SOME ARE USEFULL...**

GEORGE BOX

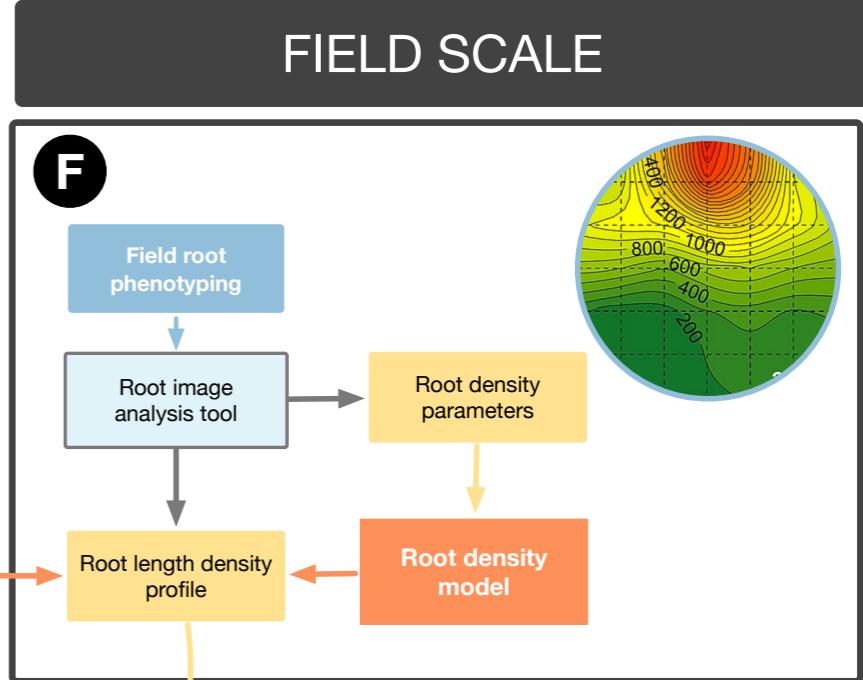
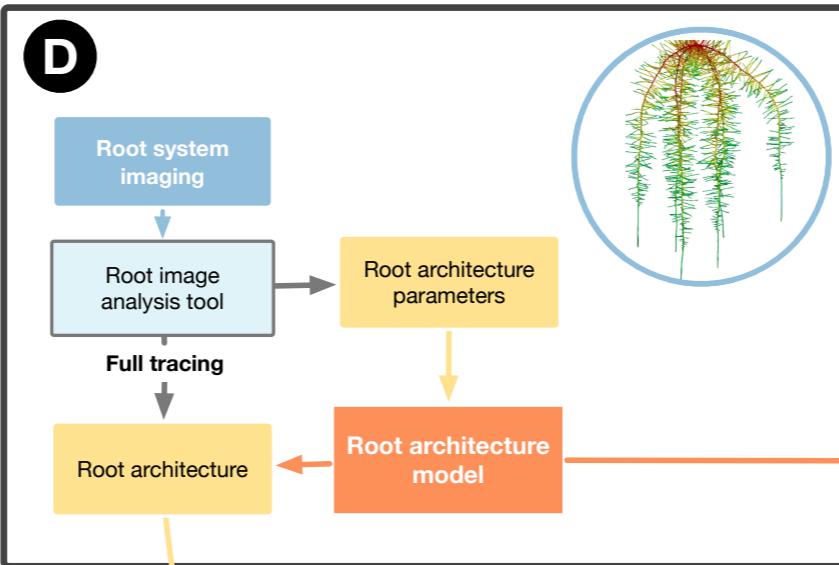
WHY DO WE NEED MODELS?

- ▶ Theory testing
- ▶ Experimental design
- ▶ Sensitivity analysis
- ▶ ...

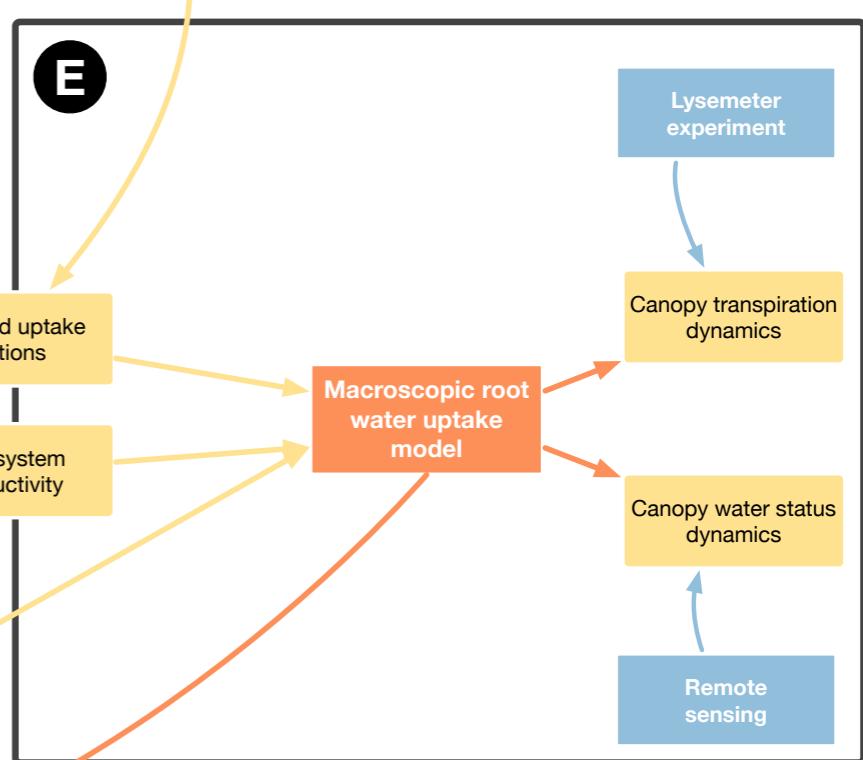
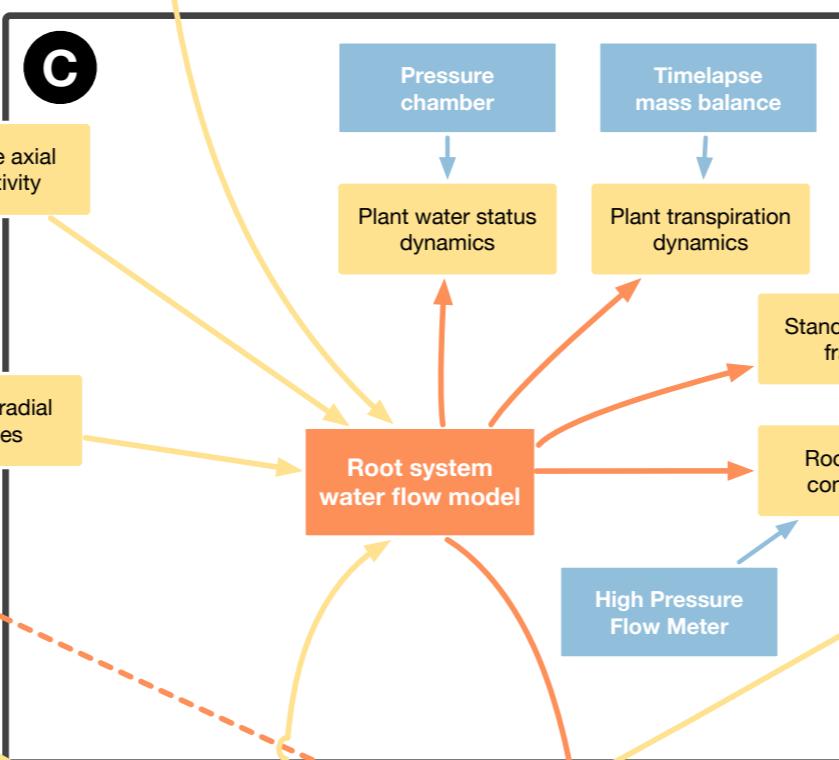
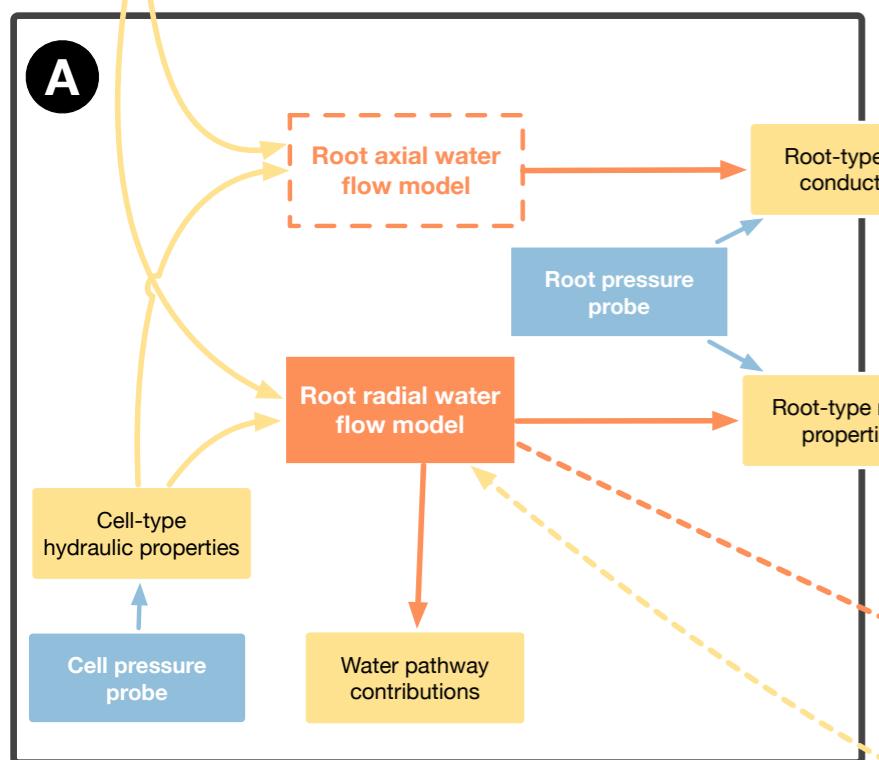
ORGAN SCALE



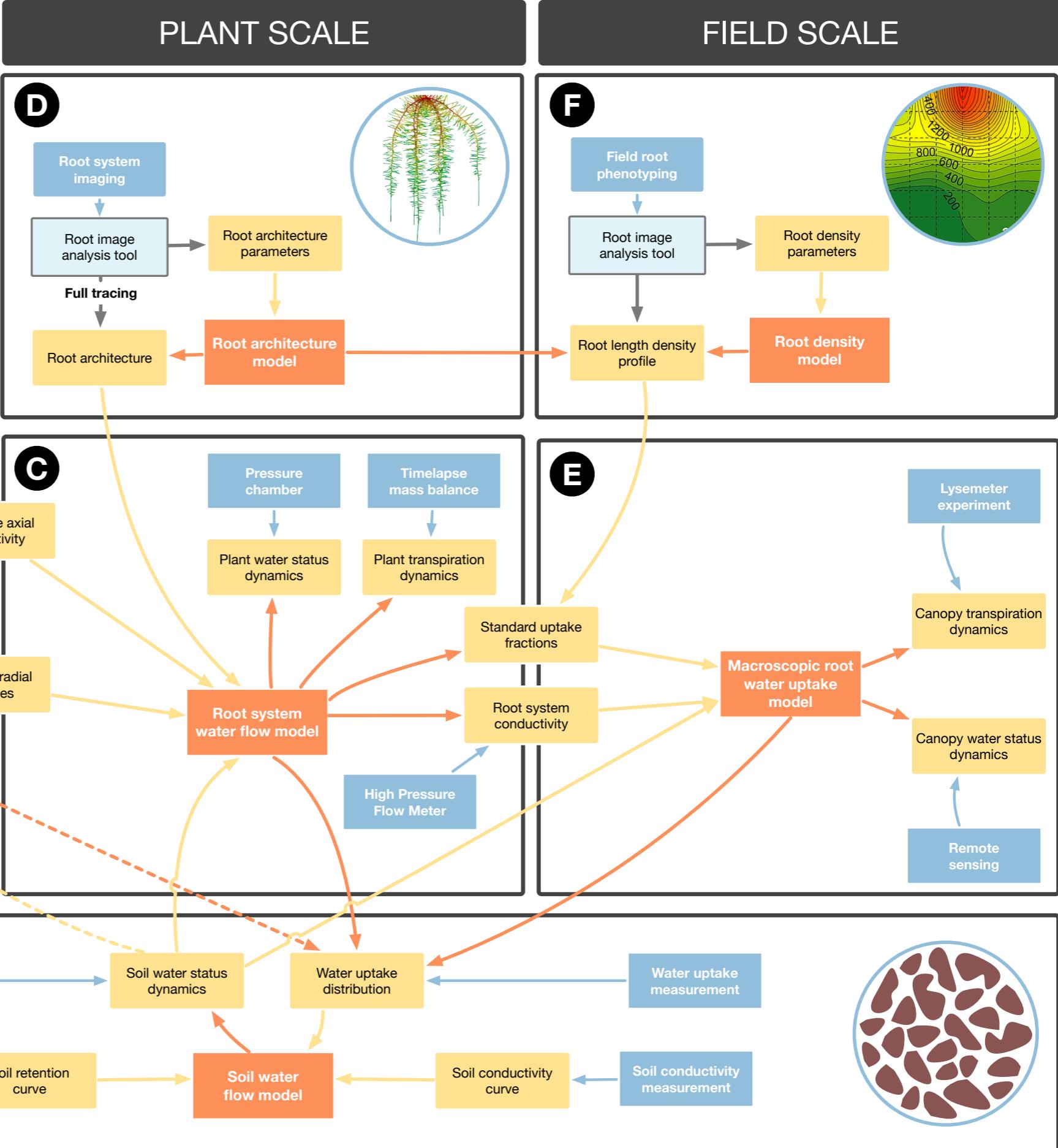
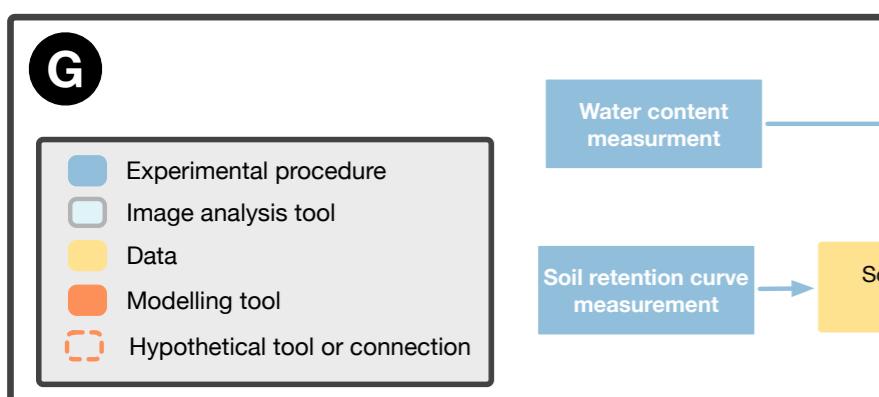
PLANT SCALE



STRUCTURE



FUNCTION

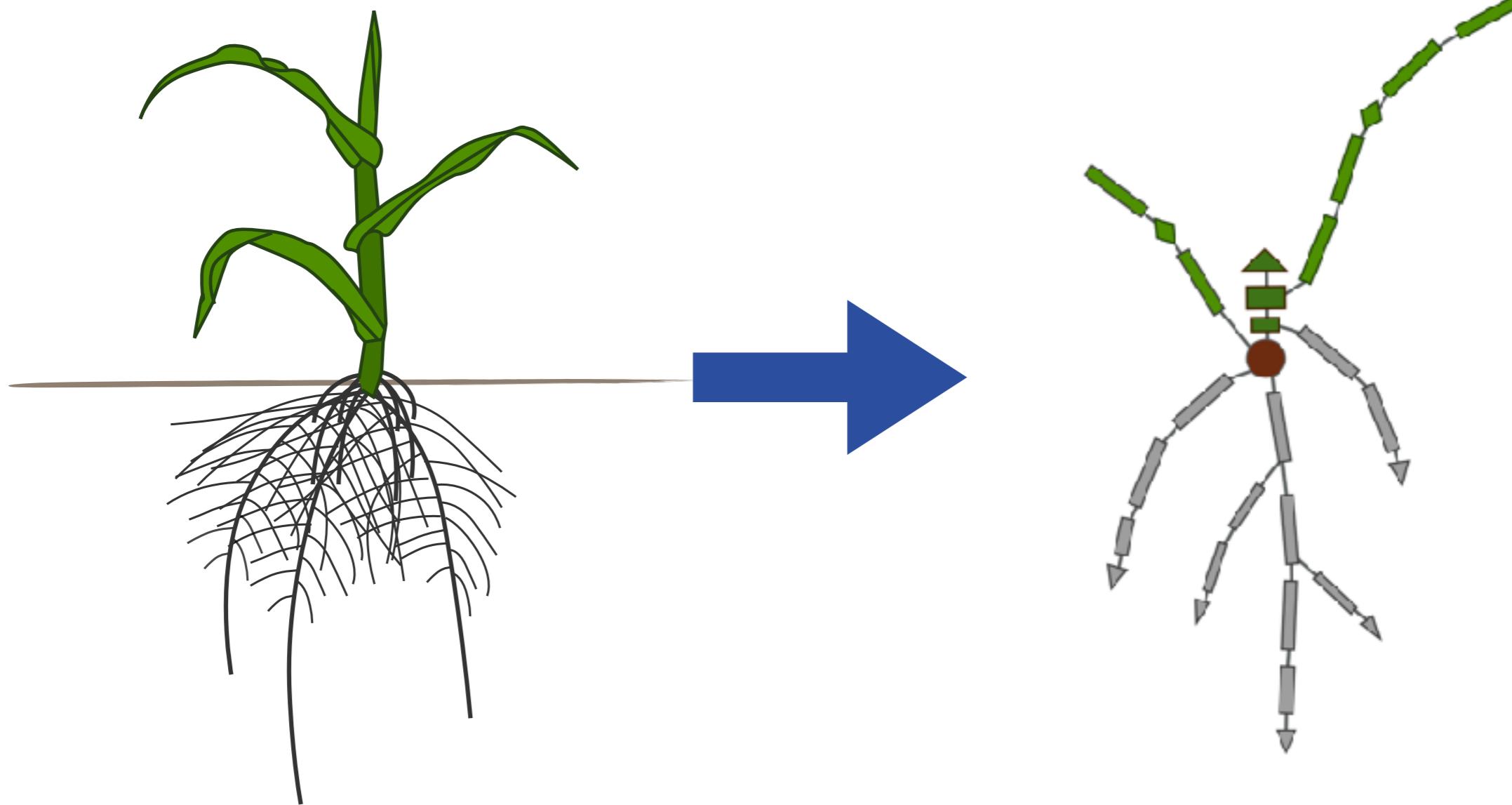


SOIL

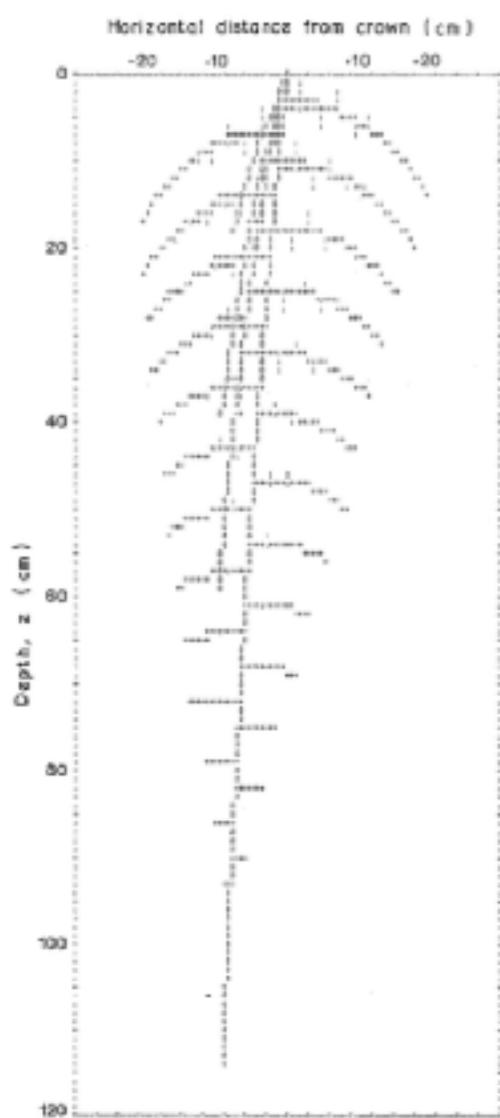
STRUCTURAL MODELLING

Represent the structure (and growth) of the root system

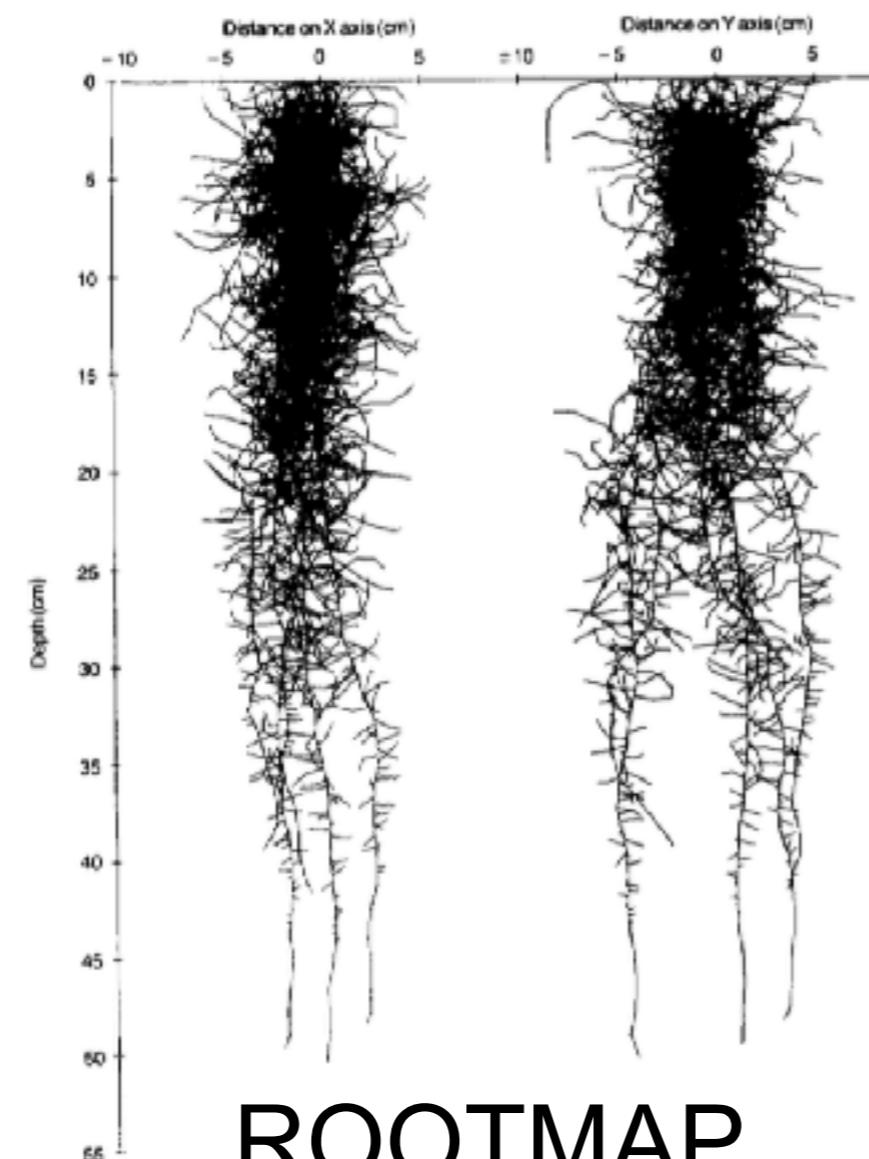
Helps you understand the dynamics (underlying processes) of the root system formation



STRUCTURAL MODELLING



1973



ROOTMAP

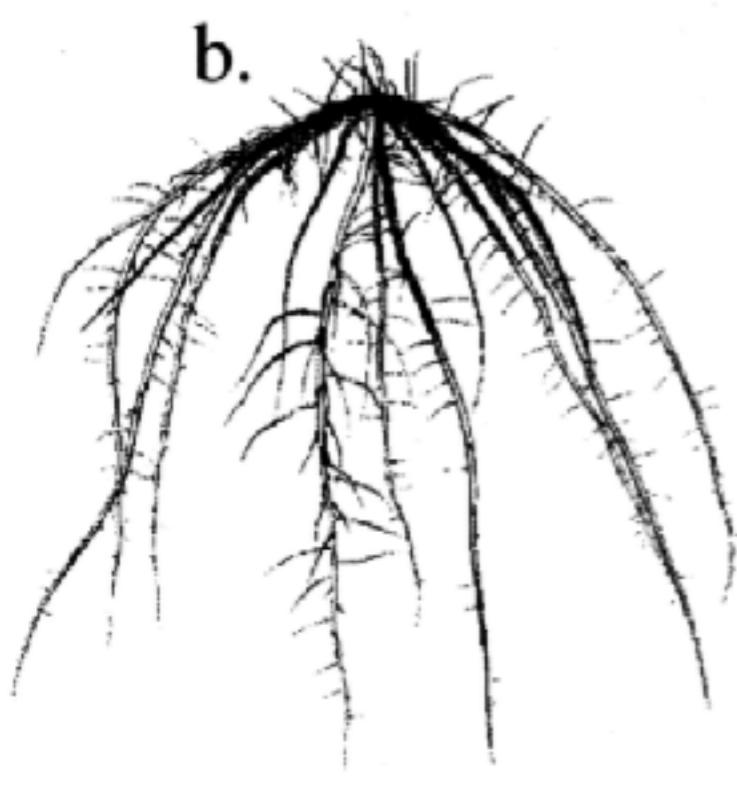
1988



1989

STRUCTURAL MODELLING

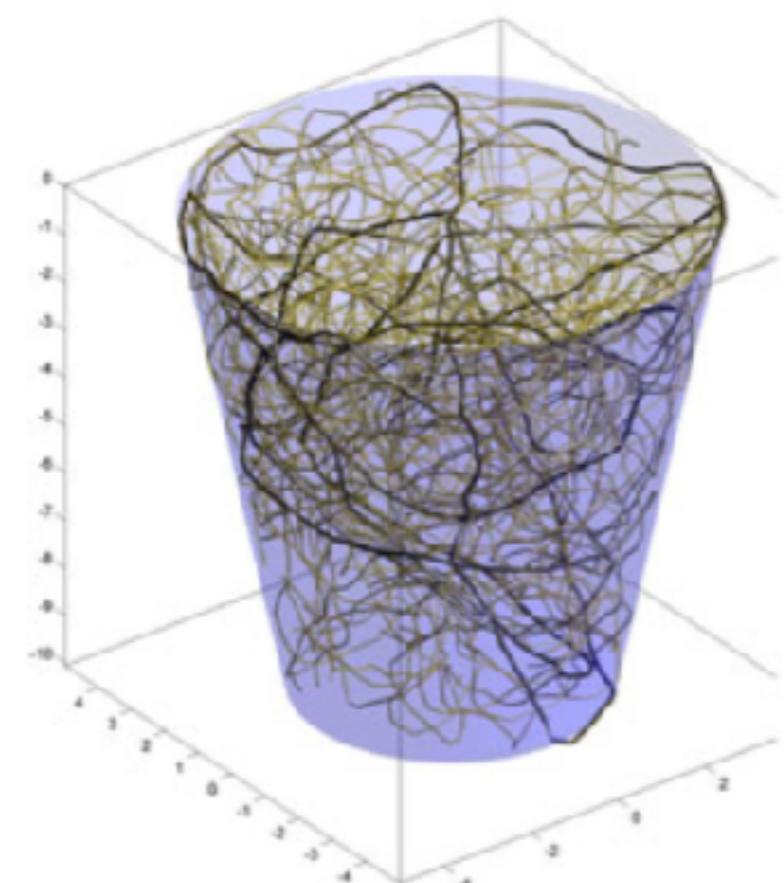
b.



1997



2004



2010

STRUCTURAL MODELLING

<http://bit.ly/crootbox>

This app displays the capabilities of the CRootBox model. Choose a dataset, unleash CRootBox, then try changing the parameters.

Forschungszentrum Jülich GmbH

1. Load parameter set

1. Select root system dataset

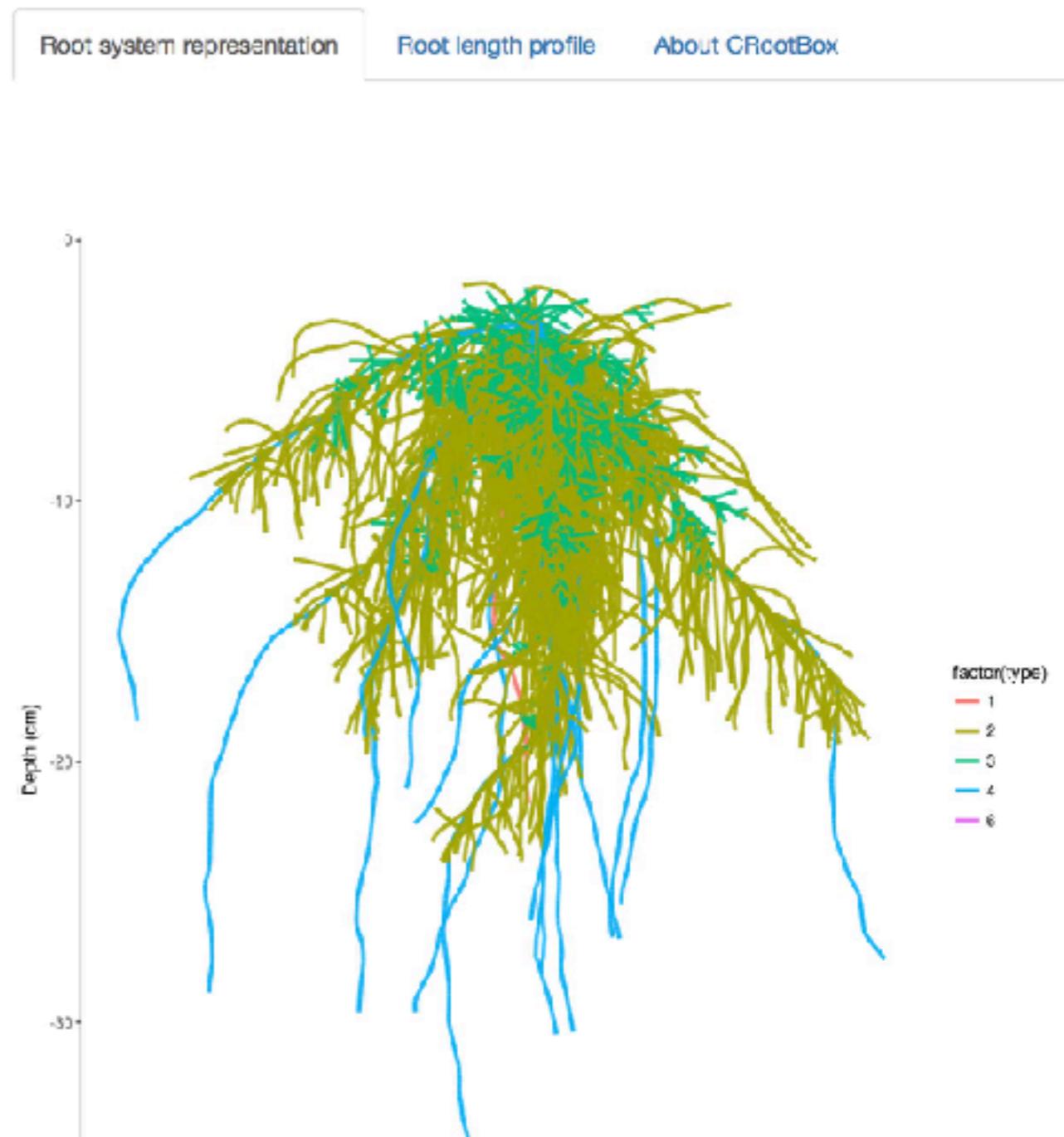
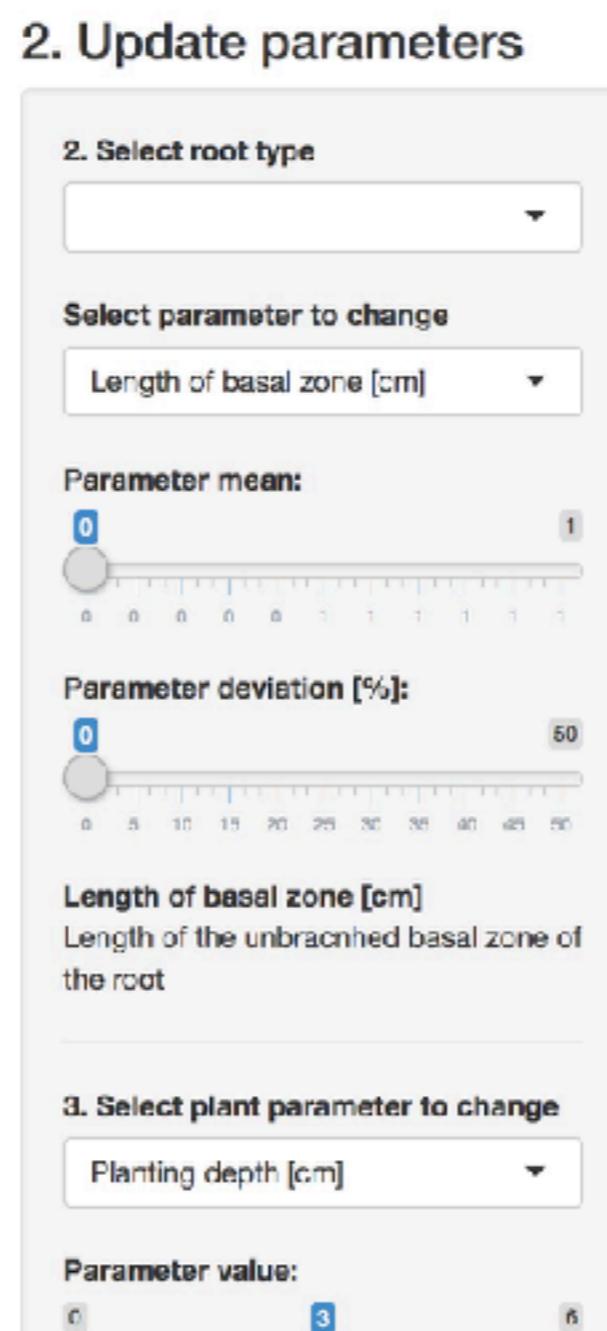
Triticum aestivum a ▾

**Simulation of wheat growth using the
3D root architecture model
SPACSYS: Validation and sensitivity
analysis**

Bingham I.J., Wu L.

European Journal of Agronomy, 34,
181-189, 2011

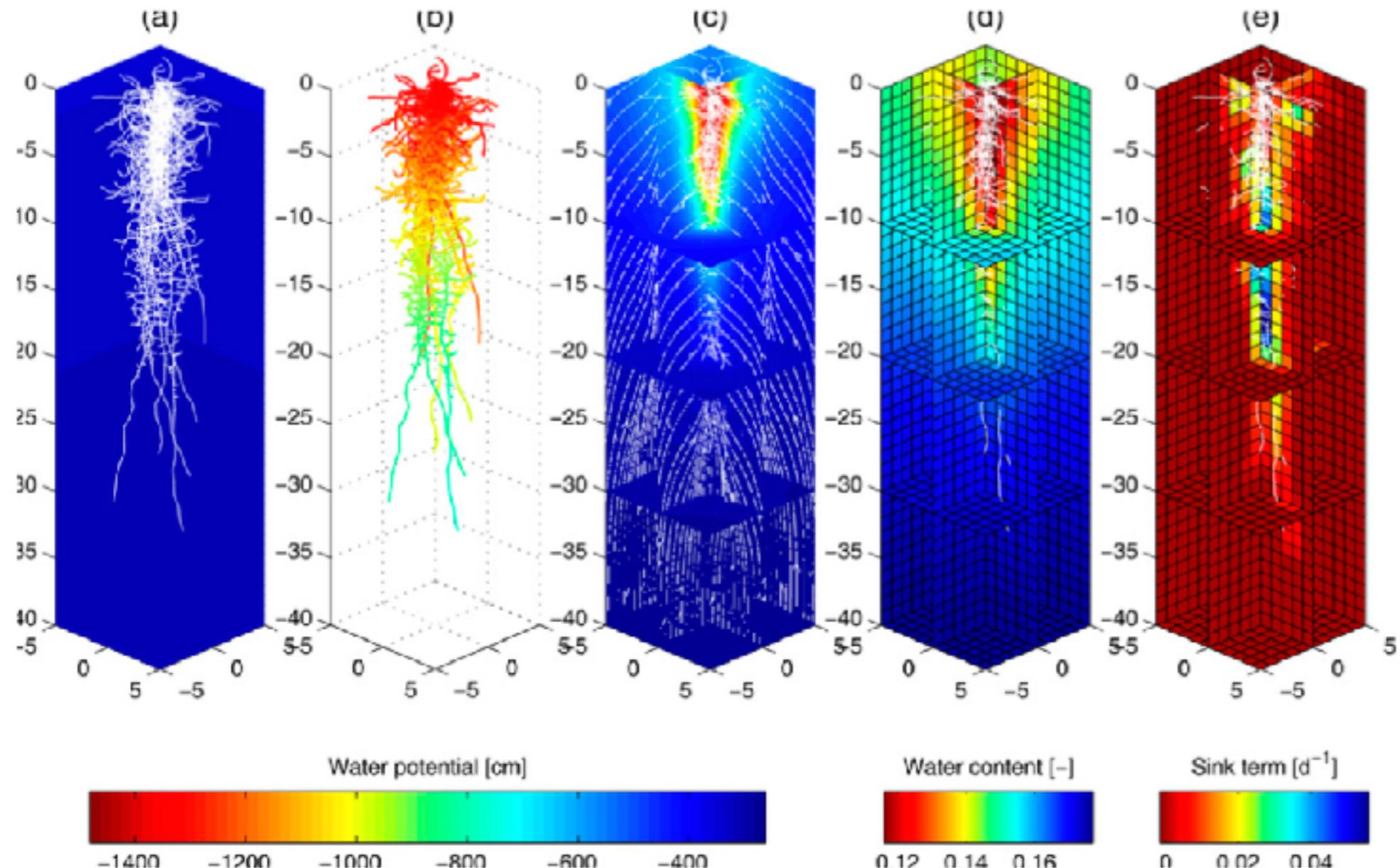
[View paper](#)



FUNCTIONAL-STRUCTURAL MODELLING

Adding function to the structure

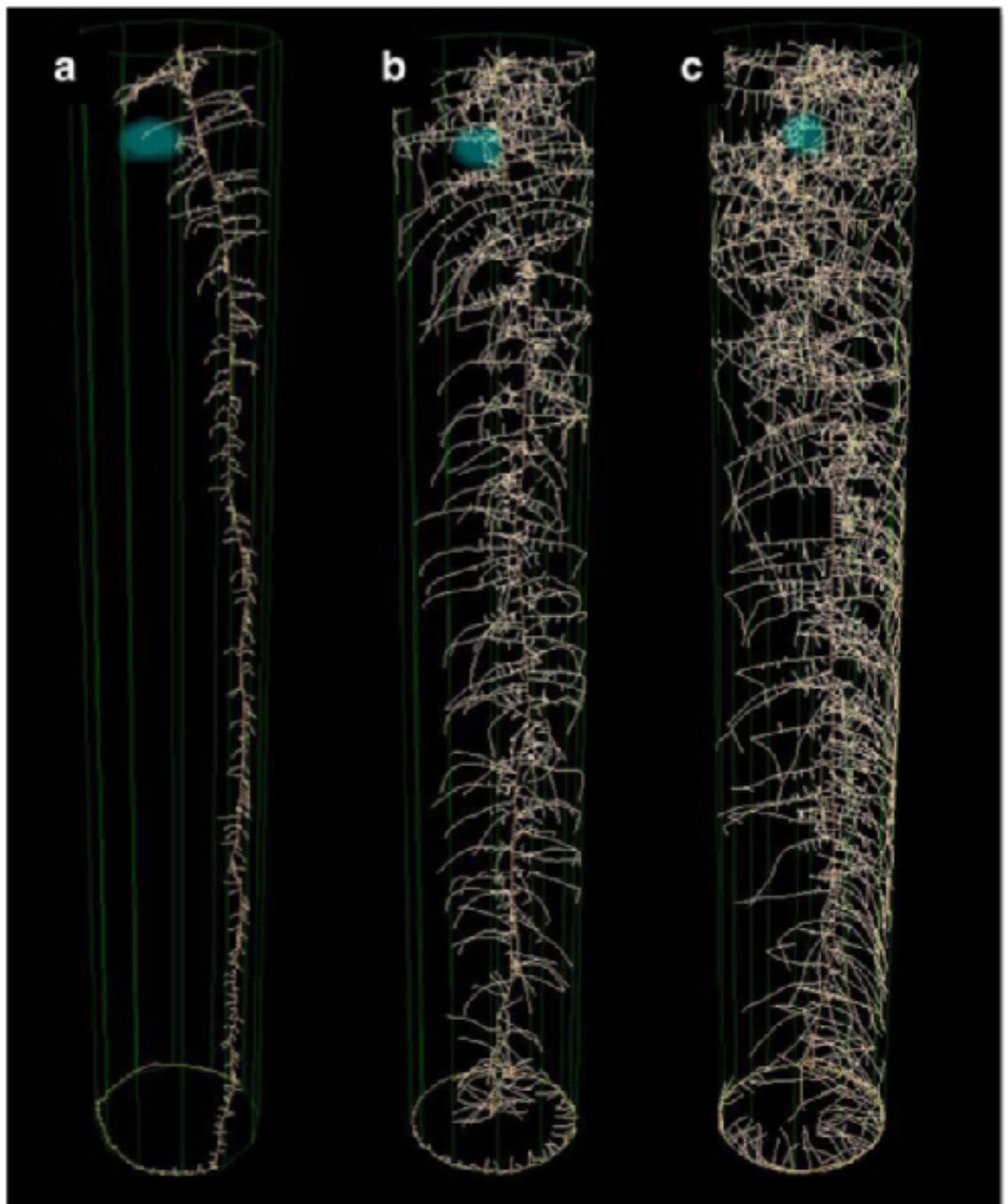
Water uptake



FUNCTIONAL-STRUCTURAL MODELLING

Adding function to the structure

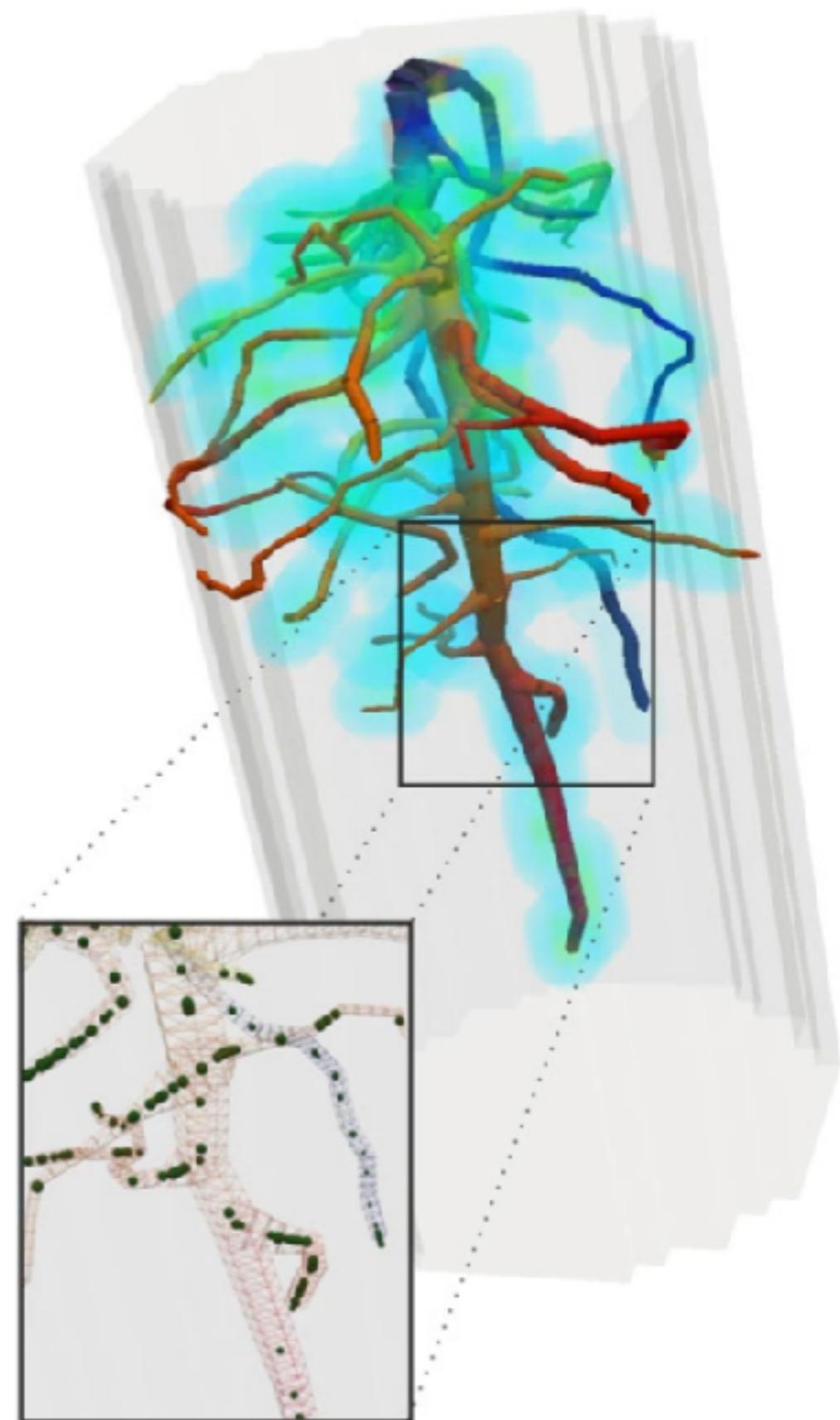
Nutrient uptake



FUNCTIONAL-STRUCTURAL MODELLING

Adding function to the structure

Transport



FUNCTIONAL-STRUCTURAL MODELLING

<https://plantmodelling.shinyapps.io/mecha/>

MECHA - Model of Explicit Cross-section Hydraulic Anatomy

Valentin Courvoisier, Marc Roger, Guillaume Loyer, Mathieu Jourde, François Chaumet and Xavier Draye

Université catholique de Louvain, Forschungszentrum Jülich GmbH

Choose plant Change parameters About

Choose a simulation to visualize

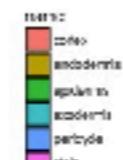
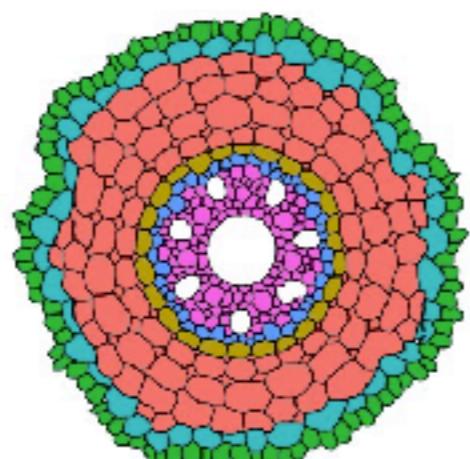
1. Select a plant type
maize-primary

MECHA was run for different cross section geometries and plant type. The results were pre-processed to be easily visualized here.



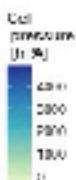
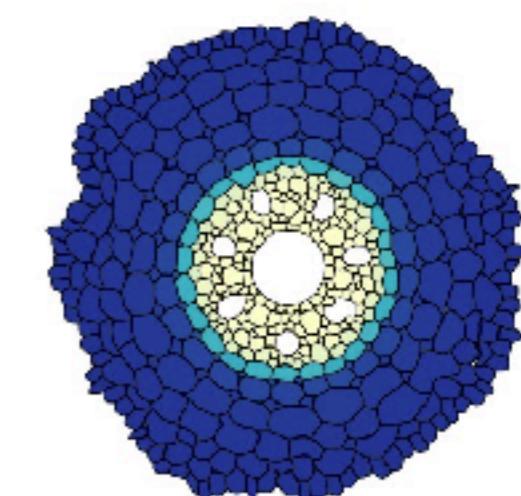
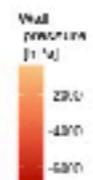
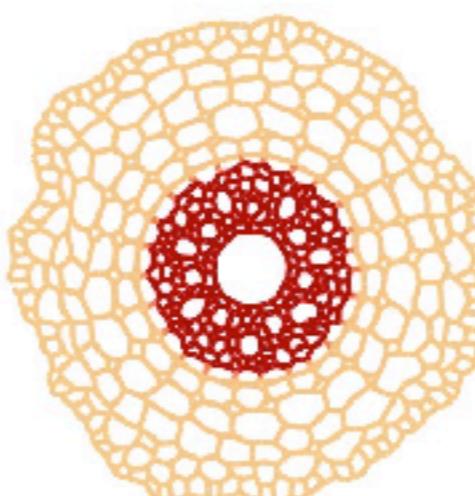
Tissue layers

Visualisation of the different cell layers used in the simulation



Cell walls pressure

Pressure within the cell walls of the cross section



Cells potentials

Pressure within the cell of the cross section

Select the information to visualize

potentials

Synthetic information about the simulation

param	value	unit
Cross-section height	0.02	cm
Cross-section perimeter	0.545	cm
Cross-section central coordinates	1.99997	mm

Display range:



Display range:

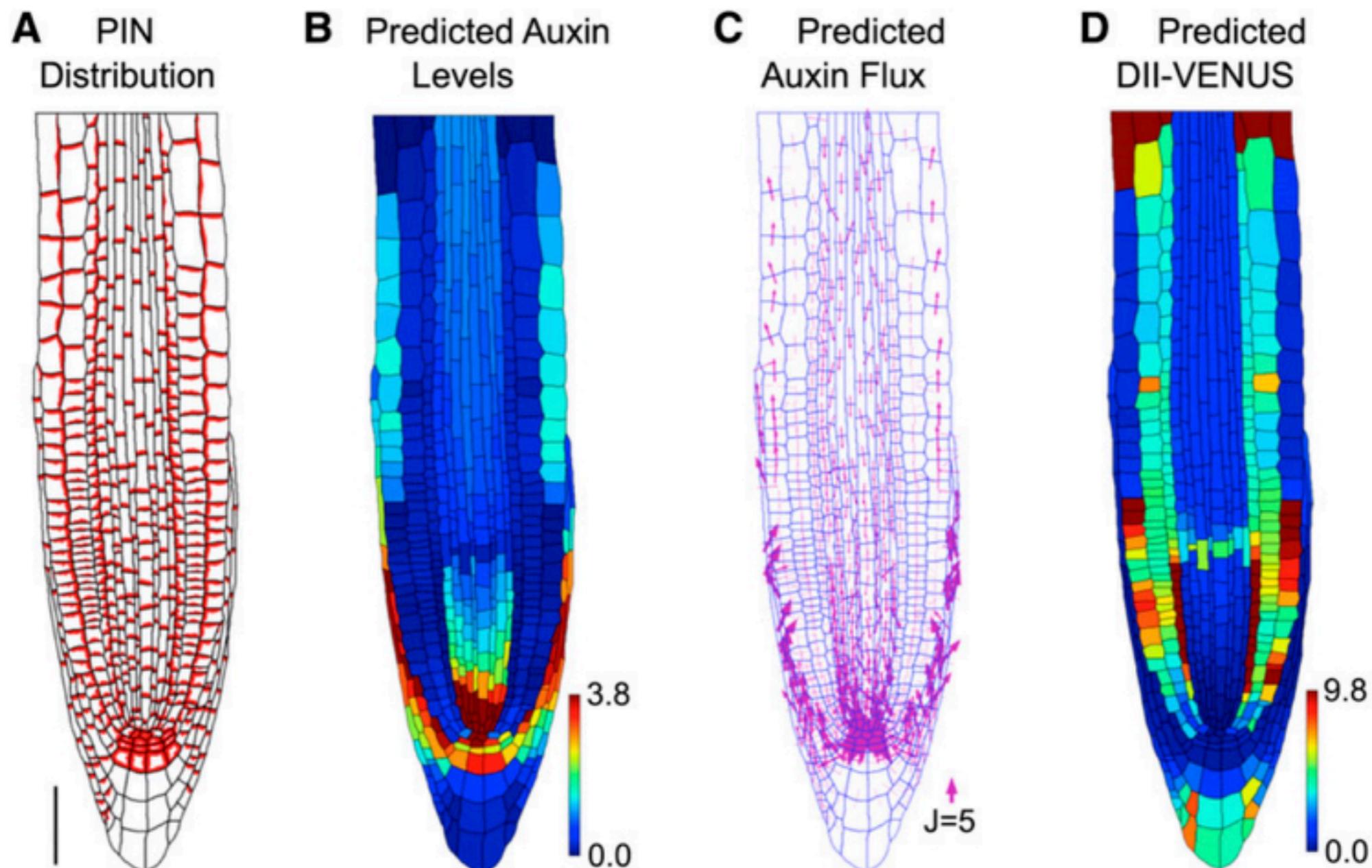


Average cell and wall pressure

Visualisation of the average cell and wall pressure across the cross-section



FUNCTIONAL-STRUCTURAL MODELLING





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4. PROJECTS

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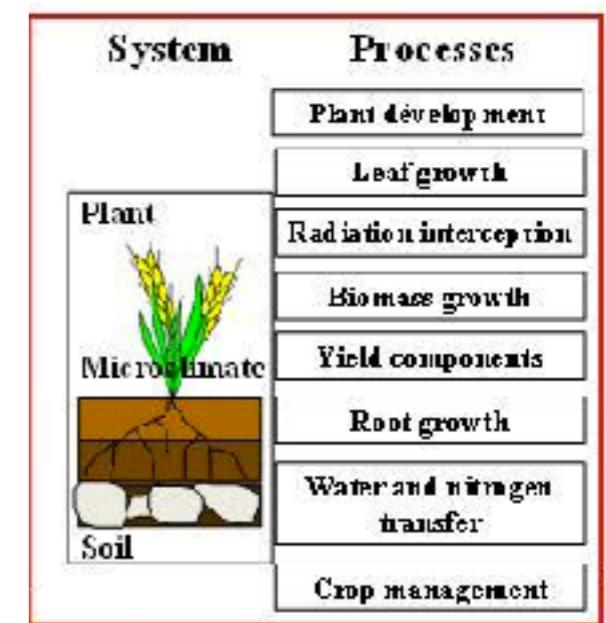
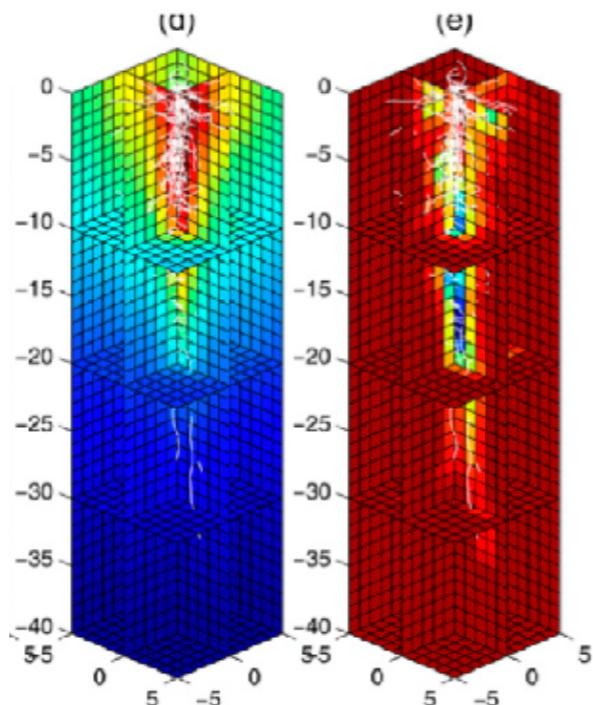
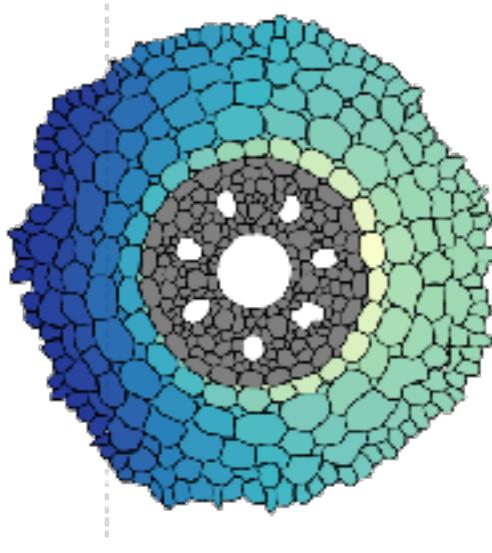
OBJECTIVES

- ▶ getting **familiar with models** in life sciences in general
(why do we need models, what can they do, what are the limitations)
- ▶ knowing **examples** of successfull models in life sciences

OBJECTIVES

- ▶ For a specific model:
 - ▶ understanding the underlying **theory** behind the model
 - ▶ understanding the **limitations** of the model
 - ▶ being able to **run** de model
 - ▶ being able to perform a **set of simulations** and interpret those
 - ▶ being able to **critisize** the model

MODELS NEARBY



MECHA

Valentin Couvreur

Xavier Draye

UCL

R-SWMS

Valentin Couvreur

Félicien Meunier

Mathieu Javaux

UCL

CROOTBOX

Guillaume Lobet

Andrea Schnepf

Daniel Leitner

UCL - Juelich

STICS

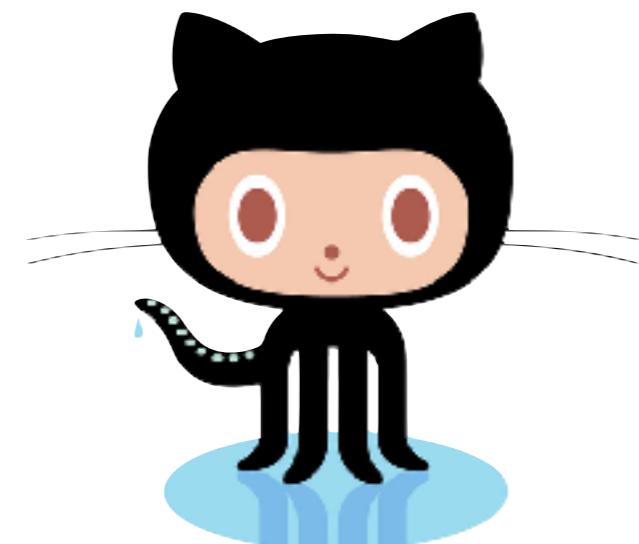
Benjamin Dumont

Gembloux

AgroBioTech

OBJECTIVES

- ▶ "Soft-skill" objectives
 - ▶ being able to **communicate** about models in life sciences to an external audience (**Twitter**)
 - ▶ being able to **collaborate** on a project (**GitHub**)



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5. GITHUB



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WHAT IS GITHUB

- ▶ Collaboration
- ▶ Version control
- ▶ Dissemination

The screenshot shows a GitHub repository page for 'archishiny'. At the top, there's a header with the repository name 'plantmodelling / archishiny', a 'Unwatch' button (1), a 'Star' button (0), and a 'Fork' button (0). Below the header, there are tabs for 'Code', 'Issues (0)', 'Pull requests (0)', 'Projects (0)', 'Wiki', 'Settings', and 'Insights'. The main content area is titled 'Shiny app for archiDART' with a 'Edit' button. It includes a section for 'Add topics'. Below that, there are summary statistics: 8 commits, 1 branch, 0 releases, and 1 contributor. A 'Branch: master' dropdown and a 'New pull request' button are also present. The main part of the page lists commit history:

Author	File	Message	Time
guillaumelabot	Added models		Latest commit 27 days ago
	www	Update the persistent homology part	27 days ago
	.gitignore	Added the possibility to view code for each plot	3 months ago
	README.md	Update README.md	3 months ago
	archiShiny.Rproj	firstcommit	3 months ago
	global.R	Added models	27 days ago
	server.R	Added models	27 days ago
	ui.R	Added models	27 days ago
	README.md		

Below the commit history, there's a section titled 'archishiny' with a description 'Shiny app for archiDART'. It provides instructions to 'To launch the app, type the following in your R console:' followed by the R code:

```
library(shiny)
shiny::runGitHub("plantmodelling/archishiny", "plantmodelling")
```

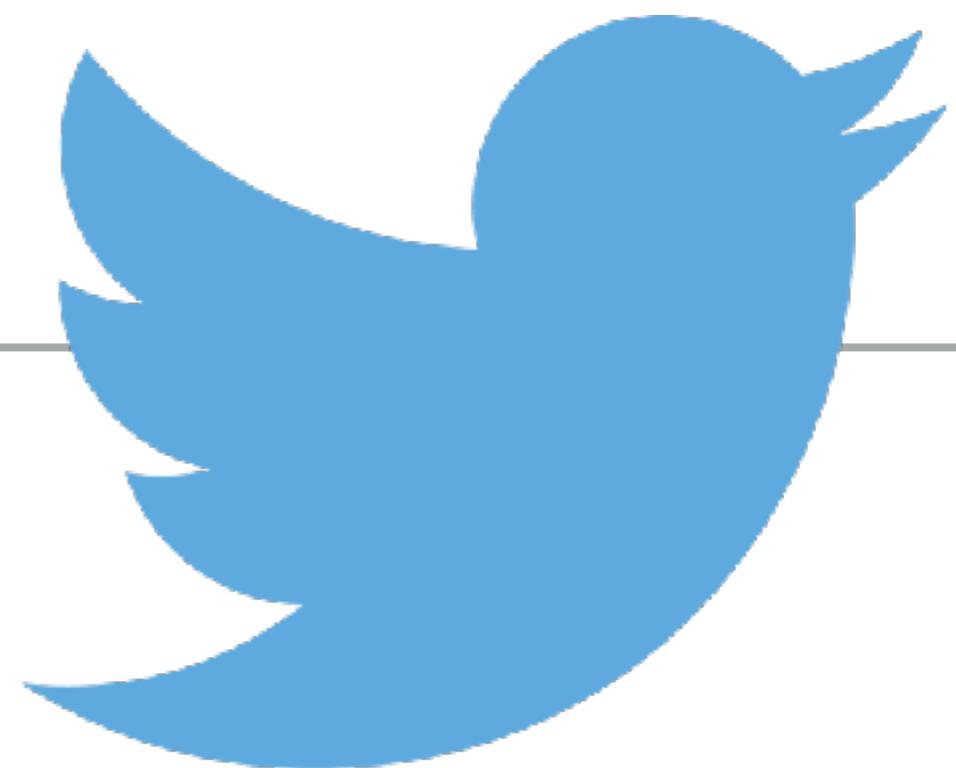
WHAT TO DO

- ▶ Create a GitHub account on www.github.com
- ▶ Download the GitHub Desktop
- ▶ Register to the course
- ▶ Clone the repo locally
- ▶ Modify the repo <https://try.github.io>
- ▶ Submit the changes

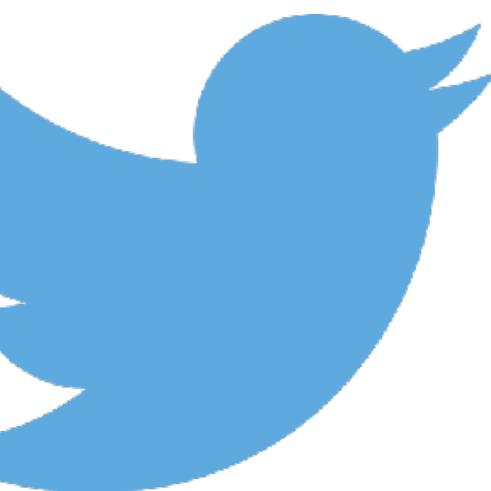
https://classroom.github.com/g/_z0dxyTS

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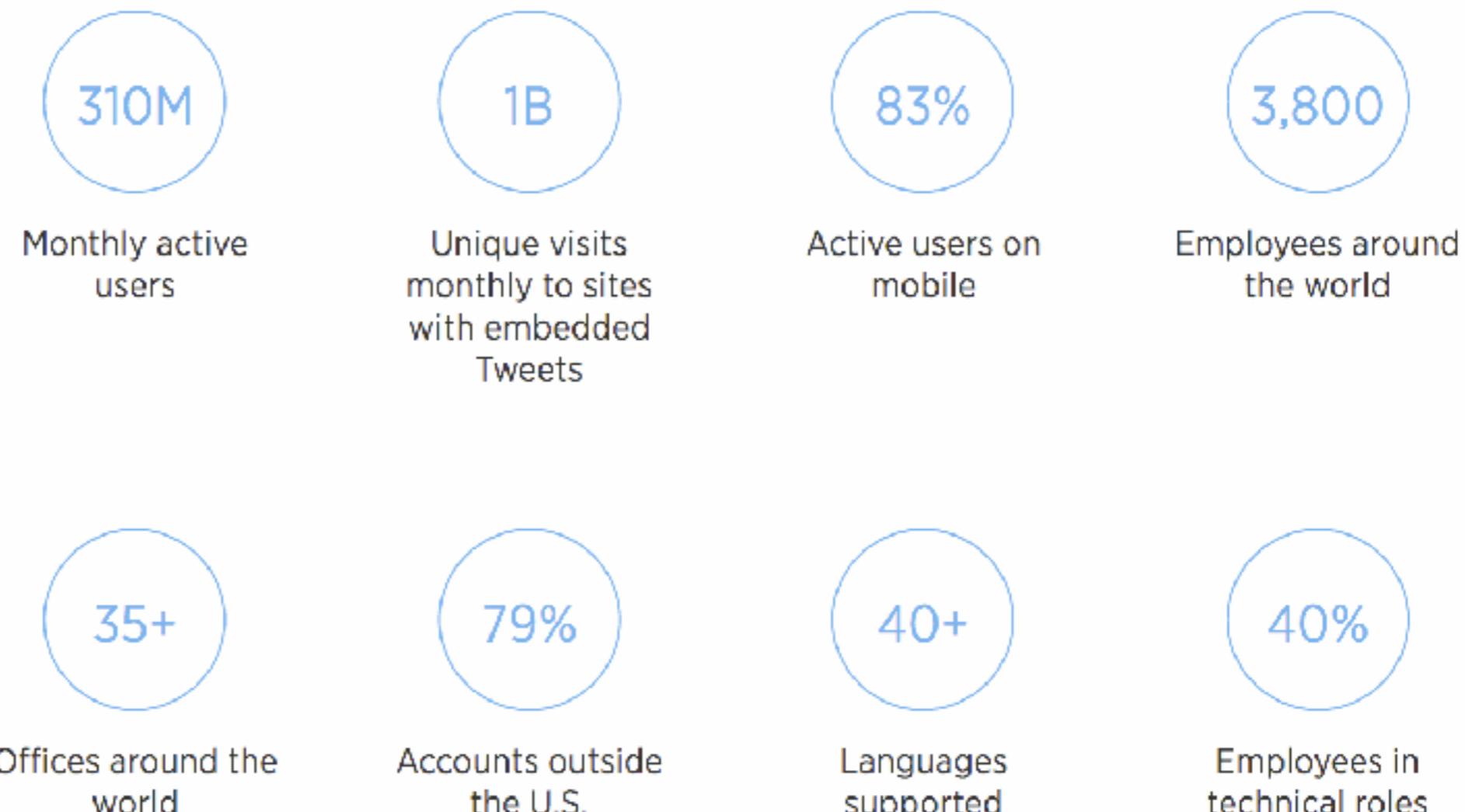
6. TWITTER



X. DRAYE & G. LOBET



8th largest
website
worldwide



All numbers approximate as of March 31, 2016.

DO SCIENTISTS REALLY USE TWITTER?

Astrophysics



Neil deGrasse Tyson

@neiltyson

4.55M

Developmental biology



David Shiffman

@WhySharksMatter

24.8K

Neurology



Oliver Sacks

@OliverSacks

113K

Evolution



Charles Darwin

@cdarwin

21.7K

DO SCIENTISTS REALLY USE TWITTER?



Philippe Baret
@PhilippeBaret
728 followers



Mathieu Javaux
@MaJavx
128 followers



Guillaume Lobet
@guillaumelobet
1019 followers



Damien Debecker
@deuxbeck
3162 followers



Earth and Life Institute
@ELI_UCLouvain
167 followers



Faculté des bioingénieurs
@AGROLouvain
1013 followers



UCL
@UCLouvain_be
3966 followers

PROFILE

You bio.

Guillaume Lobet
@guillaumelobet

May the #Roots be with you!
@UniversiteLiege @FNRS
#OpenScience #SciComm

Belgium
guillaumelobet.be
Joined January 2013
Born on December 20, 1984

117 Photos and videos

TWEETS 1,224 FOLLOWING 437 FOLLOWERS 479 LIKES 798 LISTS 3 Edit profile

Tweets [Tweets & replies](#) [Media](#)

Pinned Tweet
Guillaume Lobet @guillaumelobet · Mar 2

For anyone working in #plant #phenomics, check out call for papers for new @GigaScience serie! cc @rrellanálvarez

Call for papers

Plant Phenomics: Data integration and Analyses

Guest Editors: Rubén Rellán Álvarez & Guillaume Lobet

GIGA SCIENCE  华大基因 

Guillaume Lobet @guillaumelobet · 2h

Guillaume Lobet @guillaumelobet

Who to follow · Refresh · View all

Plant Energy Biology @Plan...  Follow

Bebatrix Kiddo @bebatrixkiddo  Follow

Find friends

Trends · Change

#ForgottenWomen

#stoking

#kdg2016

#hautekidat

#securityEU18

#nmbs

#FHfivedays

#mljntreinrjdt

#TNWEurope

#transport

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Discover · #Friends · Archive · Help

You tweets.

HOME

Tweets of
people
you follow

The screenshot shows the Twitter homepage with a red arrow pointing from the text "Tweets of people you follow" to the "Who to follow" sidebar. The main feed is highlighted with a red box.

Who to follow - Rollback - View all

- Graham Steel @McDawg** Follow
- Doctor PMS @Doctor_PMS** Follow
- AP Stylebook 🇺🇸 @APStylebook...** Follow

Find friends

© 2016 Twitter About Help Terms Privacy Cookies Ads Info Brand Blog Status Apps Jobs Businesses Media Developers Advertise with Twitter

What's happening?

Science Grrl @Science_Grrl 2m Have a good day!

Helen Mason @helen_hm11 @Science_Grrl @royalsociety Workshop on solar physics. @UKSolarPhysics #iemaphysicist

Scott Chamberlain @ckottie 3m Wikipedia OABot github.com/dissemin/oabot - Adding links to full text in Wikipedia references. #WikiCite

Perel lab @PerelLab 6m Development is for life

the Node @the_Node RT @Dev_Journal: There are many good reasons to choose Development. Find out more here: dev.biologists.org/content/six-go...

Home Notifications Messages

Search Twitter

Tweet

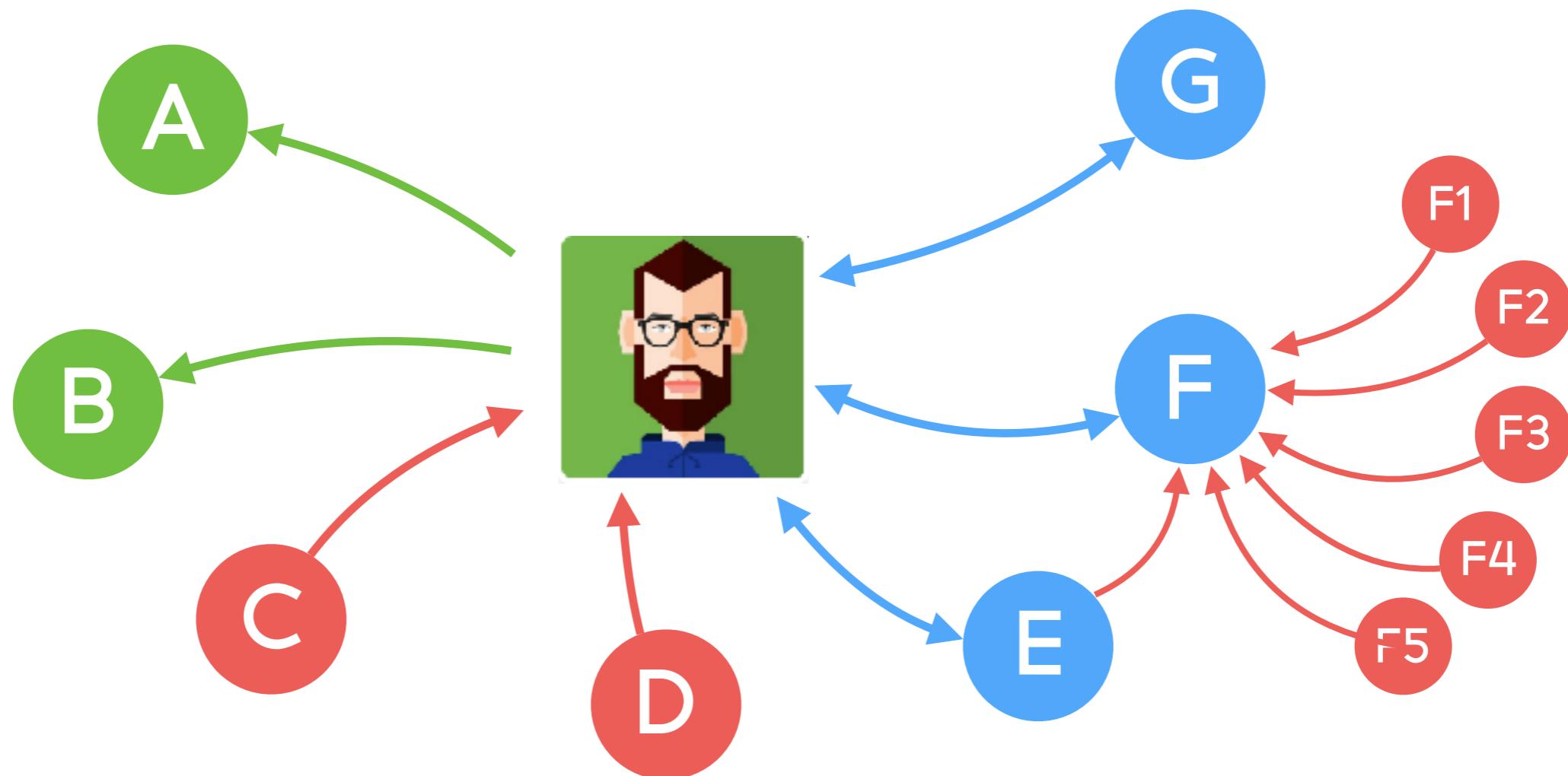
Guillaume Lobet @guillaumelobet

TWEETS 1,224 FOLLOWING 437 FOLLOWERS 479

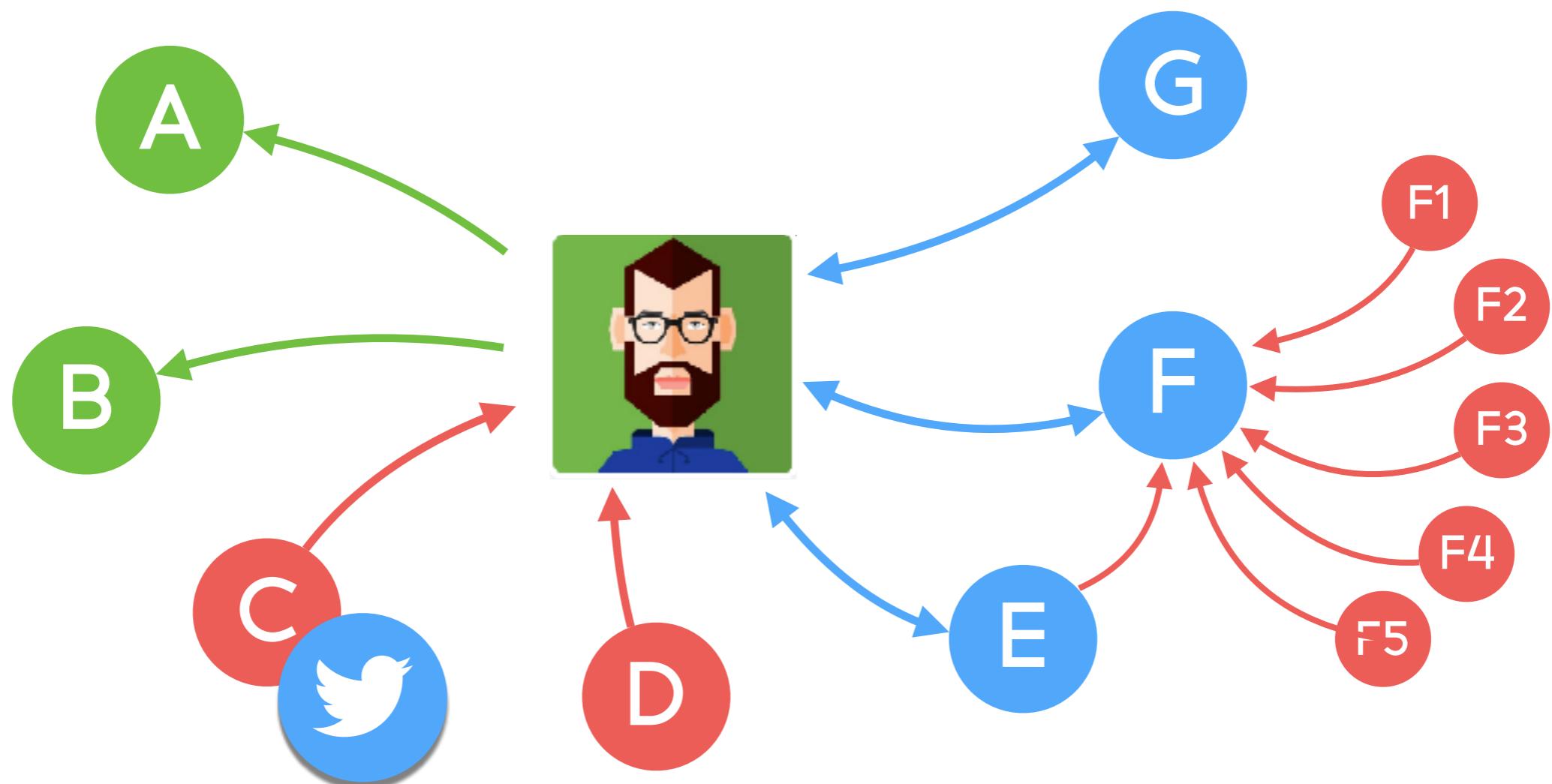
Trends · Change

- #ForgottenWomen
- #hautekiet
- #stalking
- #nmbs
- 1,398 Tweets
- #securityEU16
- #kfg2016
- #mijntreinrijdt
- #Edu4Inclusion
- #FHfivedays
- #transport
- 1,647 Tweets

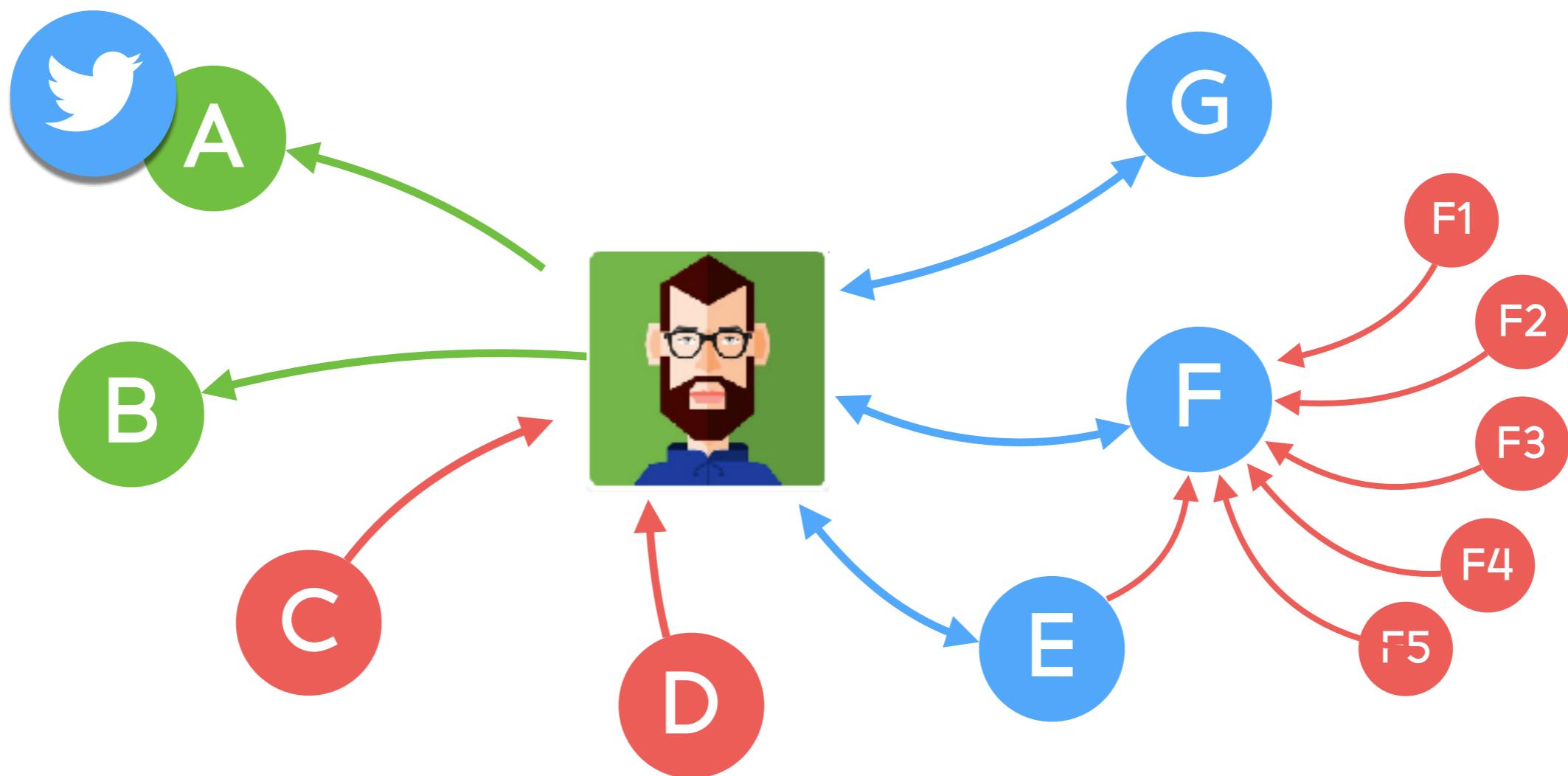
FOLLOWERS – FOLLOWING



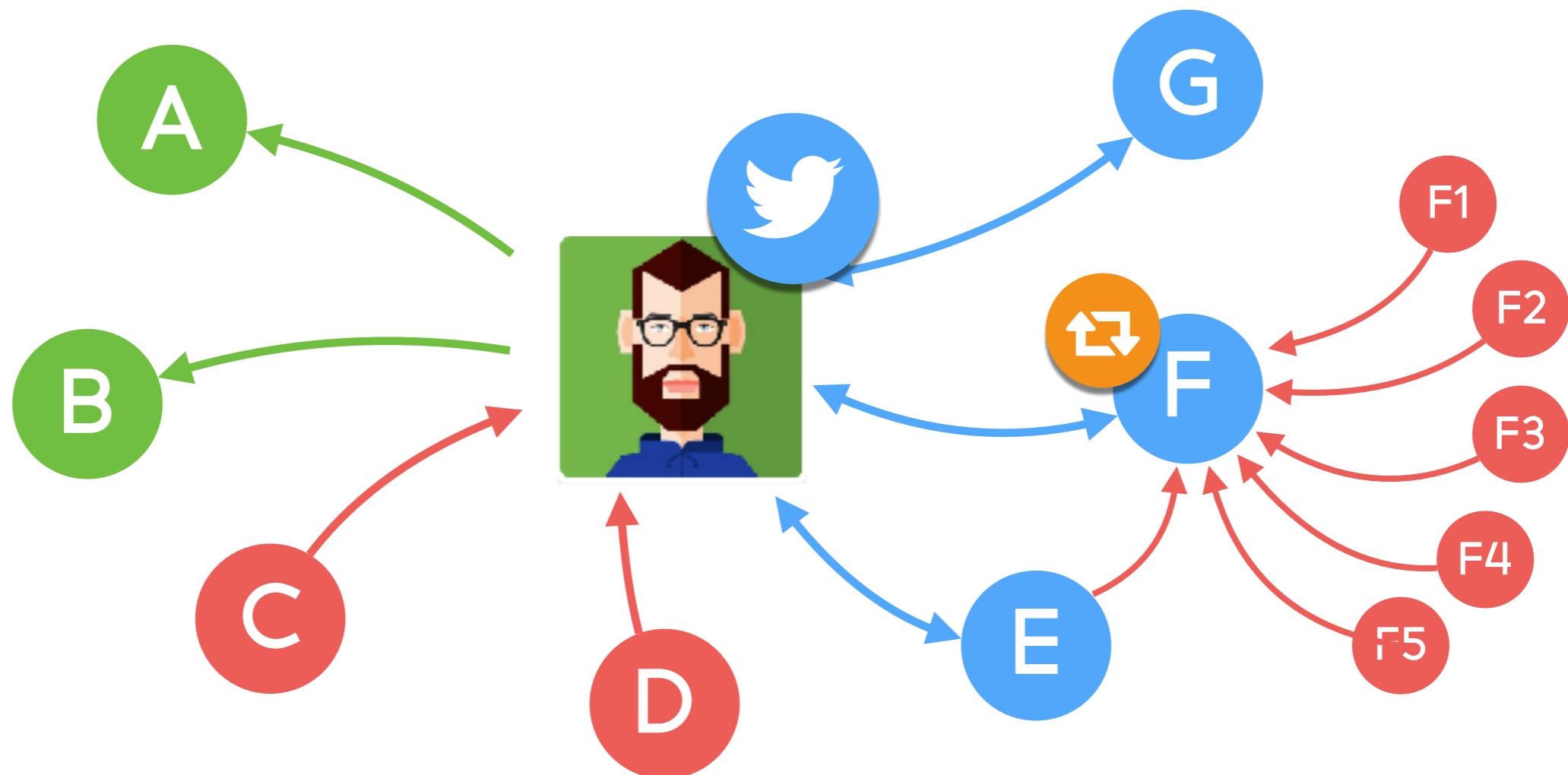
FOLLOWERS – FOLLOWING



FOLLOWERS – FOLLOWING



FOLLOWERS – FOLLOWING



EVERYBODY CAN SEE YOUR PROFILE



A composite image showing a Twitter profile picture of a man with a beard and glasses, overlaid on a background of black root structures.

Guillaume Lobet
@guillaumelobet

May the #Roots be with you!
@UniversiteLiege @frsFNRS
#OpenScience #SciComm

📍 Belgium
🔗 guillaumelobet.be
📅 Joined January 2013
🕒 Born on December 20, 1984

117 Photos and videos

TWEETS 1,224 FOLLOWING 437 FOLLOWERS 479 LINES 798 LISTS 3

[Edit profile](#)

Tweets **Tweets & replies** **Media**

Pinned Tweet
Guillaume Lobet @guillaumelobet · Mar 2
For anyone working in **#plant #phenomics**,
check out call for papers for new
@GigaScience serie! cc **@rrellanalvarez**

Call for papers

Plant Phenomics: Data integration and Analyses

Guest Editors: Rubén Rellán Álvarez & Guillaume Lobet

Who to follow · Refresh · View all

Plant Energy Biology @Plan... [Follow](#)

Beatrix Kiddo @beatrixkiddo [Follow](#)

Find friends

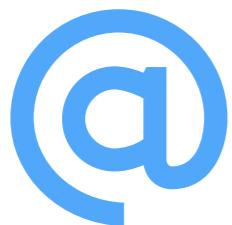
Trends · Change

#ForgottenWomen
#ataking
#kfg2016
#hautekidet
#securityEU18

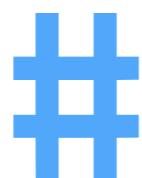
TWITTER CHEATSHEET - 1

140

characters in one tweet including pict and links.
Better use 120 to allows RT



use the handle to mention
others in your tweets.



hashtag = used to group tweets
and conversations by topics



RT @username : re-post someone else's
tweet in your thread

TWITTER CHEATSHEET - 2

REPLY

tweet in response to an other tweet
and start a conversation



if tweet starts with an handle, only this person
will see the tweet in his thread. Add a character
before the @ to make it public

LIKE

flag an interesting tweet. Used to be stars...

DM

Direct message, for private conversations.
Only for people who follow each others

TWITTER ANALYTICS

Screenshot of the Twitter Analytics dashboard for user @guillaumelobet.

Account home | **Guillaume Lobet** (@guillaumelobet) | **Page updated daily**

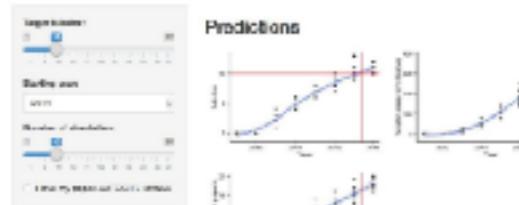
28 day summary with change over previous period

Metric	Value	Change
Tweets	23	↓34.3%
Tweet impressions	22.3K	↑33.1%
Profile visits	664	↓7.5%
Mentions	26	↓27.8%
Followers	481	↑18

May 2016 • 26 days so far...

TWEET HIGHLIGHTS

Top Tweet earned 3.3K impressions
My new blog post: #Publish more or publish better. An #h-index story. bit.ly/h-index-predict... pic.twitter.com/5TpBAKwvNN

H-INDEX PREDICTOR


Top mention earned 125 engagements
mary williams (@PlantTeaching · May 4)
2016 volume of Annu Rev Plant Biol's complete-So many authors Tweet!! annualreviews.org/toc/erplant/67... EG @mellanalvarez @JoseDinneny @guillaumelobet

ADVERTISE ON TWITTER
Get your Tweets in front of more people
Promoted Tweets and content open up your reach on Twitter to more people.
[Get started](#)

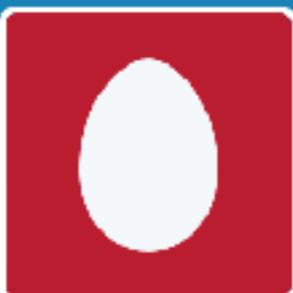
MAY 2016 SUMMARY

Metric	Value
Tweets	20
Tweet impressions	19.9K

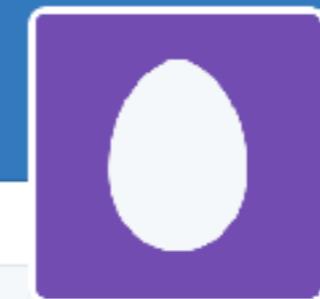
<https://analytics.twitter.com/user/username>

**TIPS
AND
TRICKS**

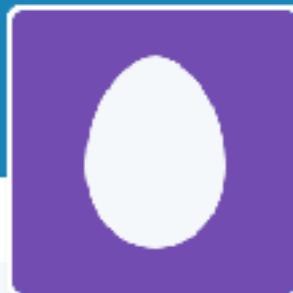
GET RID OF THE EGG!



A Twitter profile placeholder featuring a large white egg icon on a red square background. The interface includes a blue header bar, a white sidebar with a black bar at the top, and a main content area. The sidebar shows the user has joined in January 2012. The main content area displays the user's stats: TWEETS 104, FOLLOWING 2,820, FOLLOWERS 404, LIKES 10, and LISTS 2. Below the stats are three navigation tabs: Tweets, Tweets & replies, and Media. A tweet from 'andy jet @andyjet1' dated Dec 2015 is shown, reading 'It's my snow.....' with a small image of snow.



A Twitter profile placeholder featuring a large white egg icon on a purple square background. The interface includes a blue header bar, a white sidebar with a black bar at the top, and a main content area. The sidebar shows the user has joined in January 2012. The main content area displays the user's stats: TWEETS 7, FOLLOWING 154, FOLLOWERS 8, LIKES 25. Below the stats are two navigation tabs: Tweets and Tweets & replies. A tweet from 'Megan Thompson @megan_mt32' dated Dec 2015 is shown, reading 'All I can say is wow...'. Another tweet from 'LD Burnett @LDBurnett' is partially visible.



A Twitter profile placeholder featuring a large white egg icon on a purple square background. The interface includes a blue header bar, a white sidebar with a black bar at the top, and a main content area. The sidebar shows the user has joined in December 2013. The main content area displays the user's stats: TWEETS 280, FOLLOWING 106, FOLLOWERS 53, and LIKES 660. Below the stats are three navigation tabs: Tweets, Tweets & replies, and Media. A tweet from 'AKPA Retweeted' dated May 21 is shown, reading 'On Peoples and Ants: In Defense of Plants on how so working in defence of plants'.

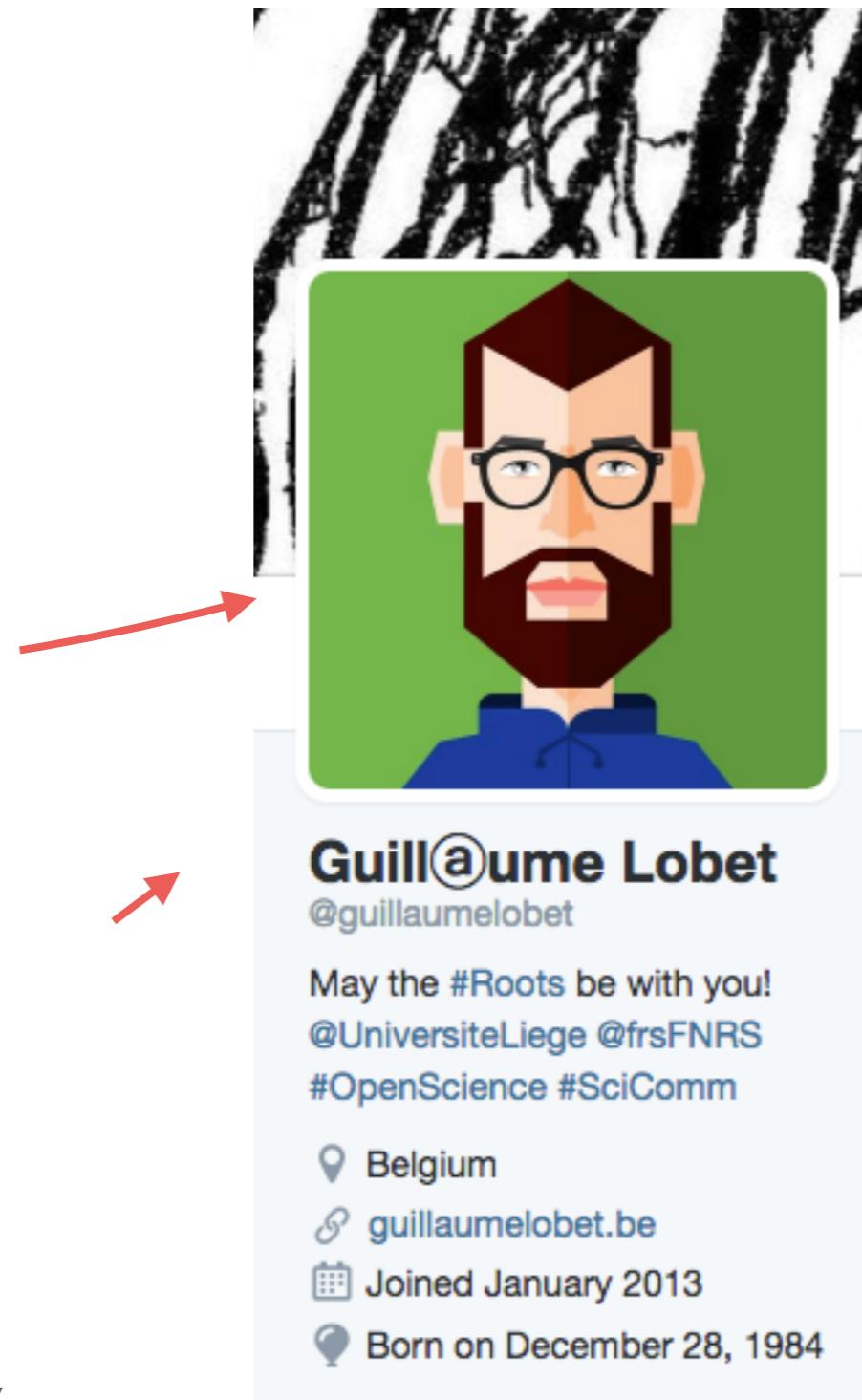


A Twitter profile placeholder featuring a large white egg icon on an orange square background. The interface includes a blue header bar, a white sidebar with a black bar at the top, and a main content area. The sidebar shows the user has joined in January 2013. The main content area displays the user's stats: TWEETS 25, FOLLOWING 1,707, FOLLOWERS 134, LIKES 12, and LISTS 1. Below the stats are two navigation tabs: Tweets and Tweets & replies. A tweet from 'salih öztürk @salih_ozturk14' dated Jan 29 is shown, reading 'Yağan yağmurda islanan saçlarımdı ama temizlenen sadece kalbim.....'.

PROFILE

Your **picture**.

- Can be changed



Your **name**.

- Can be changed
- Make it **meaningful**

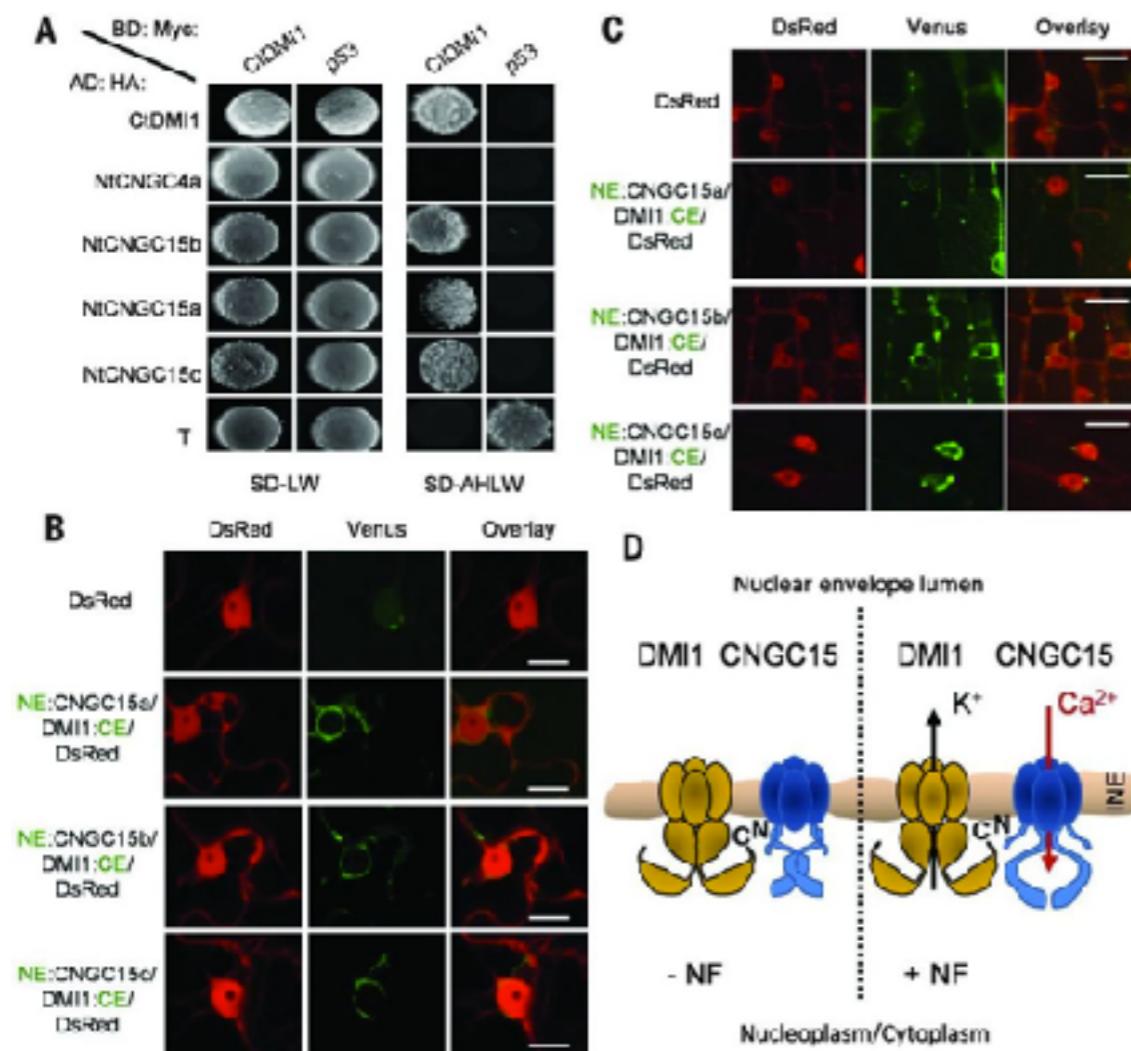
Your **handle**.

- Cannot be changed
- Make it easy
- Use your name

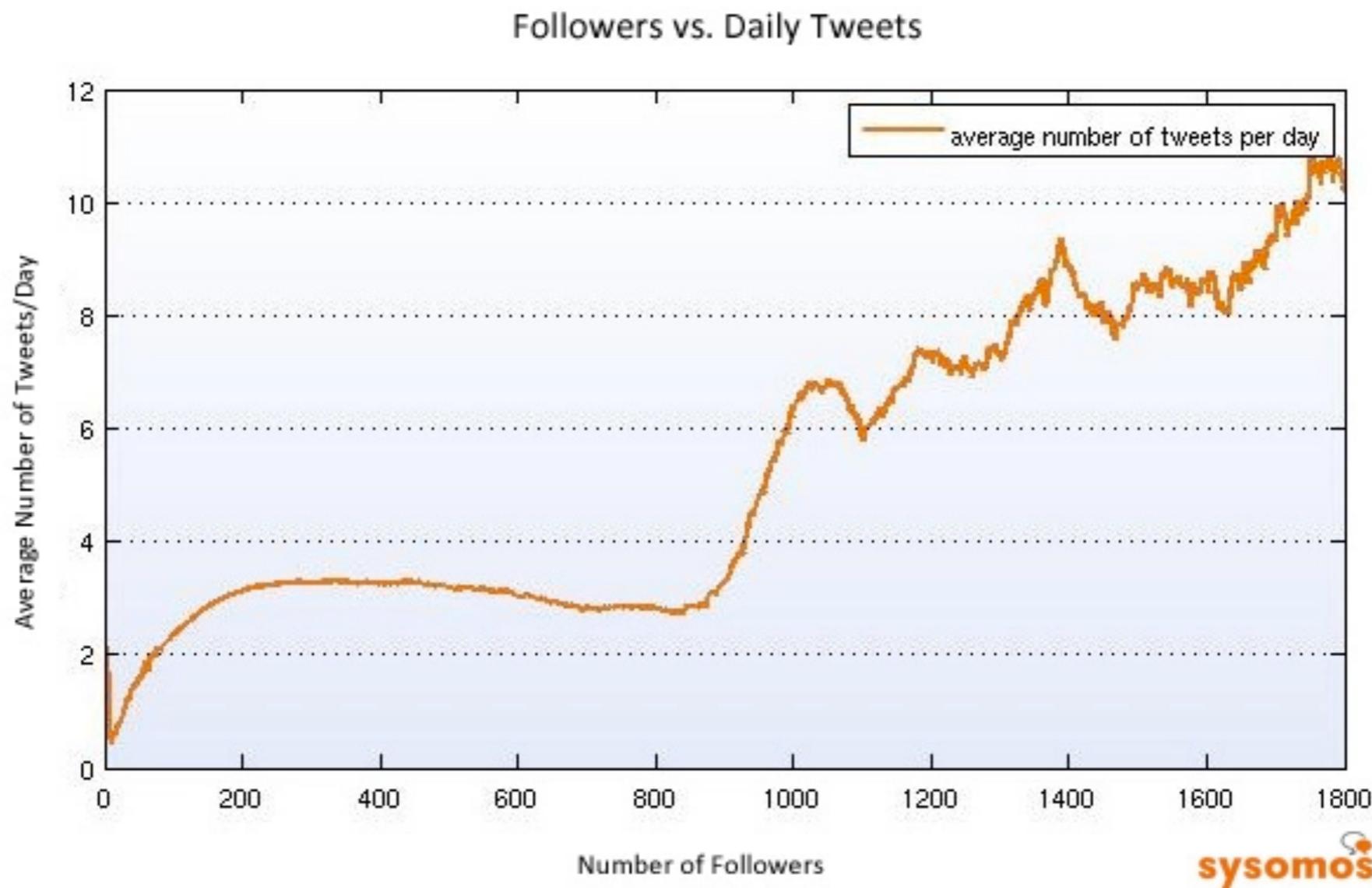
Your **bio**.

- Can be changed
- Make it **informative**

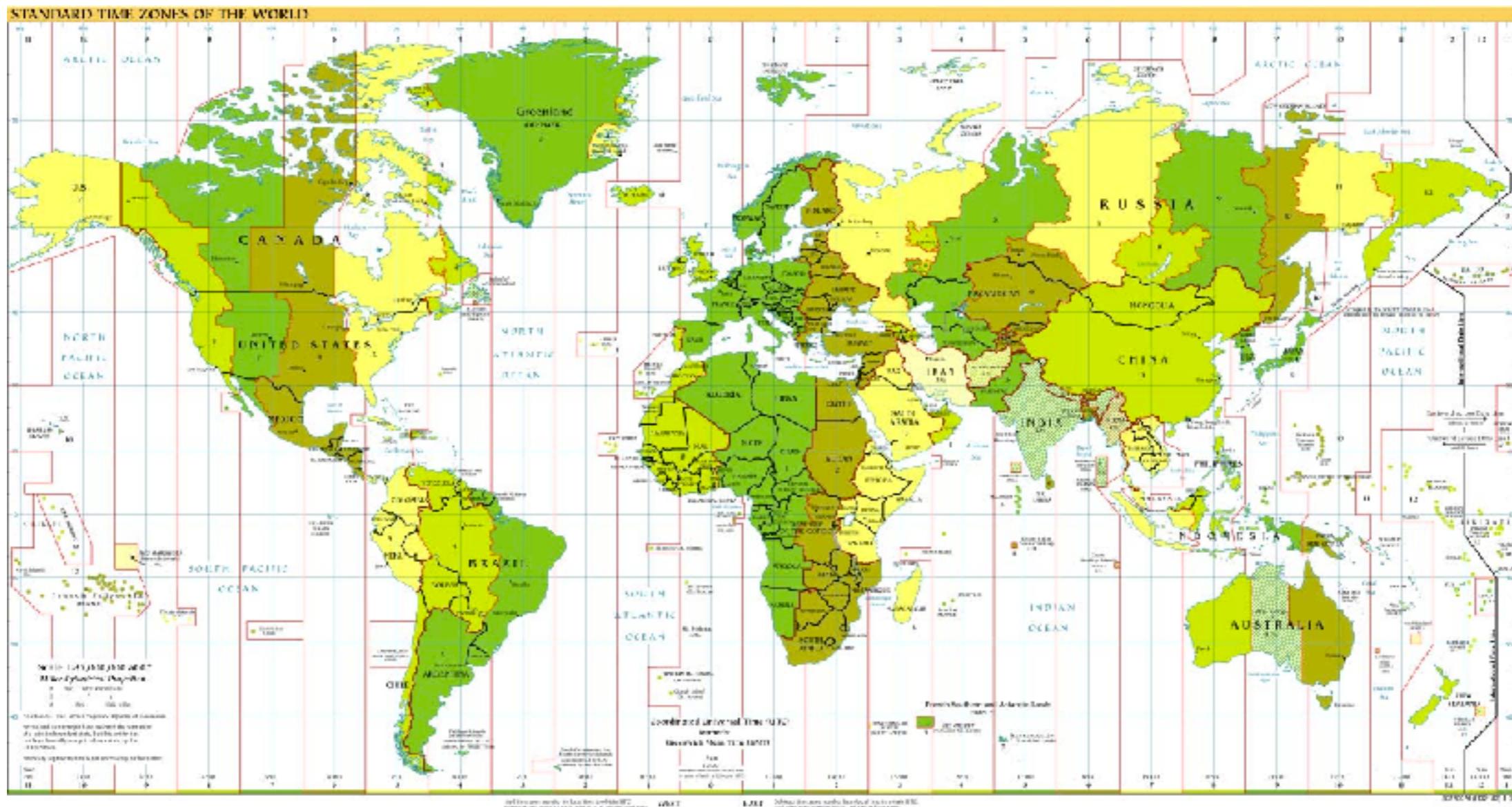
TWEETS DEFINE FOLLOWERS



TWEETS DEFINE FOLLOWERS



PLAN YOUR TWEETS FOR LARGER AUDIENCE



ENGAGE
WITH
OTHER
PEOPLE
BE NICE !

7 EFFECTIVE WAYS TO ENGAGE ON TWITTER

Twitter is an ideal tool to help you stay informed and drive traffic to social properties. Most importantly, it helps you build relationships with like-minded people. Below are tips to increase engagement with your communities on Twitter.

PROMOTE OTHERS

Make sure you retweet your most passionate followers. Thank them and link to their social properties. #FF (Follow Friday) and #Recommend others and their work.

BE THE FIRST TO BREAK THE NEWS

Your followers will come to rely on you as an expert and will foster the conversation around your tweets.



INFUSE PERSONALITY INTO YOUR PROFILE

Use a real picture of yourself and highlight your passions in your bio.

ADD IMAGES FOR BETTER IMPACT

Open Science Retweeted
Mark Dingemans @DingemansMark · 23h
High quality reviews and rapid editorial action by @maxcoltheart – our fully
#openscience paper will soon be out

Gwilym Lockwood @GwilymLockwood
EHP paper accepted at @CollabroOA and will be out (along with the data
and analysis scripts) as soon as the copyediting is done.

JPascal van Ypersale Retweeted
Climate Council @climatecouncil · 0h
Science censorship: #GreatBarrierReef scrubbed from UN #climatechange
report bit.ly/IVkJDtp #reefgate

In reply to Randy Daniels
Kevin Folta @kevinfoalta · 3h
. @DaneelOlivaw12 Read my blog tomorrow. Death of a Sock Puppet. You had
all the balls in the world until you had to step up. Leave me alone

In reply to Randy Daniels
Kevin Folta @kevinfoalta · 3h
. @DaneelOlivaw12 and you guys harass me about transparency? Step up or
step out, but don't lecture me from behind a mask.

USE URL SHORTENERS

[https://www.dropbox.com/s/8z2a4gv8q2phamw/
20160527_social_media.pdf?dl=0](https://www.dropbox.com/s/8z2a4gv8q2phamw/20160527_social_media.pdf?dl=0)



<http://bit.ly/lobet-social-media>

WHAT TO DO:

- ▶ Create 2 groups
- ▶ Choose a name for the group / twitter account
- ▶ Define the *editorial* lines
- ▶ Create the twitter account (www.twitter.com)
- ▶ Personalise the profile page
- ▶ Start tweeting

SAVE YOUR TWEETS ON STORIFY

As seen on [plantmodelling.xyz](#)

Twitter reviewing + response

Live reviewing by Larry M York of a bioRxiv pre-print + reply from Guillaume Lobet

by  Guillaume Lobet · a year ago · 23 views ·

Thumbnail for [Using a structural root system model for an in-depth assessment of root image analysis pipeline](#)

Root system analysis is a complex task, often performed using fully automated image analysis pipelines. However, these pipelines are usually evaluated with a limited number of ground-truth root images, most likely of limited size and complexity. We have used a root model, *RootSim*, to create a large and diverse library of ground-truth root system images.

 bioRxiv

 **Larry M. York**
@LarryMallYork



Replying to @guillaumelobet
Interesting and useful concept of synthetotype a bit confusing.
simulation parameter set is more like a genotype 1/n
8:16 PM · Sep 16, 2016

1 2 3

 **Larry M. York**
@LarryMallYork



Replying to @LarryMallYork @guillaumelobet
the 10 outcomes of that simulation parameter set are more like phenotypes as influenced by 'environmental' conditions 2/n
8:19 PM · Sep 16, 2016

2 3 4

<https://storify.com>