Package 'MILC'

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Title MIcrosimulation Lung Cancer (MILC) model

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Description The MILC package is designed to predict individual trajectories using the continuous time microsimulation model MILC, that describes the natural history of lung cancer.

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MILC-package *MIcrosimulation Lung Cancer (MILC) model*

Description

The MILC package is designed to predict individual trajectories describing the onset of, progression, and (potentially) death from lung cancer using the MILC continuous time microsimulation model.

Details

The MIcrosimulation Lung Cancer model (MILC), is a new, dynamic, continuous time microsimulation model that, in its current version, comprises a module that describes the natural history of lung cancer in the absence of any screening or treatment component. The model simulates the course of lung cancer from the disease free state to the local, regional, and distant states and eventually to death from either lung cancer or some other cause. When predicting individual trajectories, the model accounts for age, gender, and smoking history, including smoking status, start and quit smoking ages, and average number of cigarettes smoked per day when relevant.

The model comprises four main components:

- **Onset of the first malignant cell:** The local stage of the lung cancer tumor initiates with the onset of the first malignant cell, as described by the Two-Stage Clonal Expansion (TSCE) carcinogenesis model (see `HT_mal` for more details).
- **Tumor growth:** The model assumes a spherical tumor growth described by a Gompertz distribution (see `t_prog` for more details).
- **Disease progression:** Given a Gompertzian tumor growth, the tumor volume at specific time points is described by log-Normal distributions (see `t_prog` for more details).
- **Survival:** The model employs the Cumulative Incidence Function (CIF) non-parametric technique to simulate survival in a competing-risks frame.

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Author(s)

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Gray, B. (2013) cmprsk: Subdistribution Analysis of Competing Risks, URL: http://CRAN.R-project.org/package=cmprsk. R package version 2.2-6.

`age_grp` *Define age group*

Description

Returns the 5-year age group ("<40", "40-44", ..., or "85+" years) to which an individual belongs.

Usage

```
age_grp(age)
```

Arguments

`age`	continuous variable in years.

Value

Factor indicating the 5-year age group.

Author(s)

Stavroula A. Chrysanthopoulou

See Also

d_grp

Examples

```
# 5-year age group of an individual 21 years old:
  age_grp(21)
# 5-year age group of an individual 77.5 years old:
  age_grp(77.5)
```

---

ci.lung *ci.lung dataset*

Description

An R object of class "list" containing Cumulative Incidence Function estimates for lung cancer mortality, by age (5-years age group), gender ("male" or "female") and tumor stage at diagnosis (i.e., "localized", "regional", or "distant").

Usage

```
ci.lung
```

Format

The *'ci.lung'* list comprises 68 components in total. Each component itself is an R object of class "list" with three components, i.e.:

[[1]] a vector with time points (in years)

[[2]] a vector with CIF estimates

[[3]] a vector with variances of the CIF estimates

Source

CIF estimates are derived using data obtained from the Surveillance, Epidemiology, and End Results (SEER) database covering the years 1973-2008.

See Also

current.other, former.other, never.other

Examples

```
data(ci.lung)
ci.lung[1]
ci.lung[[1]][1] # time (years)
ci.lung[[1]][2] # CIF estimates
ci.lung[[1]][3] # variances of CIF estimates
```

`current.other` *current.other dataset*

Description

An R object of class "list" containing Cumulative Incidence Function estimates for other cause (not lung cancer) mortality, for current smokers by age (5-years age group), gender ("male" or "female") and smoking intensity group ("1-10", "11-20", or "21+" cigerettes) based on the average number of cigarettes smoked per day.

Usage

```
current.other
```

Format

The *'current.other'* list comprises 66 components in total. Each component itself is an R object of class "list" with three components, i.e.:

[[1]] a vector with time points (in years)

[[2]] a vector with CIF estimates

[[3]] a vector with variances of the CIF estimates

Source

CIF estimates are derived using data obtained from the National Health Interview Survey (NHIS) database covering the years 1986-2004.

See Also

`ci.lung`, `former.other`, `never.other`

Examples

```
data(current.other)
current.other[1]
current.other[[1]][1] # time (years)
current.other[[1]][2] # CIF estimates
current.other[[1]][3] # variances of CIF estimates
```

d_grp *Define smoking intensity group*

Description

Returns the smoking intensity group ("1-10", "11-20", or "21+" cigarettes) of an individual based on the average number of smoked per day.

Usage

```
d_grp(d)
```

Arguments

d	continuous variable indicating smoking intensity (number of cigarettes).

Value

Factor indicating the smoking intensity group.

Author(s)

Stavroula A. Chrysanthopoulou

See Also

age_grp

Examples

```
# Specify the smoking intensity group of an individual who smokes:

# 1 cigarette/day:
  d_grp(1)

# 22 cigarettes/day:
  d_grp(22)
```

former.other *former.other dataset*

Description

An R object of class "list" containing Cumulative Incidence Function estimates for other cause (not lung cancer) mortality, for former smokers by age (5-years age group), gender ("male" or "female") and smoking intensity group ("1-10", "11-20", or "21+" cigarettes) based on the average number of cigarettes smoked per day.

Usage

```
former.other
```

Format

The *'former.other'* list comprises 22 components in total. Each component itself is an R object of class "list" with three components, i.e.:

[[1]] a vector with time points (in years)

[[2]] a vector with CIF estimates

[[3]] a vector with variances of the CIF estimates

Source

CIF estimates are derived using data obtained from the National Health Interview Survey (NHIS) database covering the years 1986-2004.

See Also

ci.lung, current.other, never.other

Examples

```
data(former.other)
former.other[1]
former.other[[1]][1] # time (years)
former.other[[1]][2] # CIF estimates
former.other[[1]][3] # variances of CIF estimates
```

HT_mal *Calculate cumulative hazard for the 1st malignant cell*

Description

Cumulative hazard up to age t for the onset of first malignant cell, given gender, smoking status and smoking intensity.

Usage

```
HT_mal(t, gender, d, smok_status)
```

Arguments

t	age
gender	gender ("male", or "female")
d	smoking instensity (number of cigarettes)
smok_status	whether the individual is a smoker ("Y") or not ("N")

Details

Integration from age 0 to age t of the hazard rate h(t) for the onset of the first malignant cell, as described by the Two-Stage Clonal Expansion (TSCE) carcinogenesis model:

$$h(t) = \frac{\nu\mu X(e^{(\gamma+2B)t} - 1)}{\gamma + B(e^{(\gamma+2B)t} + 1)}$$

with $\gamma = \alpha - \beta - \mu$ and B=$\frac{1}{2}(-\gamma + \sqrt{\gamma^2 + 4\alpha\mu})$

Power laws express the effect of smoking on the hazard for the onset of the first malignant cell, given smoking intensity d at age t, i.e.:

$$\alpha = \alpha_0[1 + \alpha_1 \cdot d^{\alpha_2}] \quad \text{and} \quad \gamma = \gamma_0[1 + \alpha_1 \cdot d^{\alpha_2}]$$

where

X:	total number of normal stem cells
ν:	normal cell initiation rate
α:	division rate of initiated cells
β:	apoptosis rate of initiated cells
μ:	malignant conversion rate of initiated cells
d:	average number of cigarettes smoked per day

Value

Cumulative hazard for the onset of the first malignant cell.

Author(s)

Stavroula A. Chrysanthopoulou

References

Moolgavkar, S. H., and Luebeck, G. (1990) Two-event model for carcinogenesis: Biological, mathematical, and statistical considerations. *Risk Analysis*, 10(2):323-341.

Heidenreich, W. F., Luebeck, E. G. and Moolgavkar, S. H. (1997) Some properties of the hazard function of the two-mutation clonal expansion model. *Risk Analysis*, 17(3):391-399.

Hazelton, W. D., Clements, M. S. and Moolgavkar, S. H. (2005) Multistage carcinogenesis and lung cancer mortality in three cohorts. *Cancer Epidemiology Biomarkers & Prevention*, 14(5):1171-1181.

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Meza, R., Hazelton, W. D., Colditz, G. A. and Moolgavkar, S. H. (2008) Analysis of lung cancer incidence in the nurses' health and the health professionals' follow-up studies using a multistage carcinogenesis model. *Cancer Causes & Control*, 19(3):317-328.

See Also

`ht_mal_int`, `t_mal`

Examples

```
# Cumulative hazard of the onset of the first malingant cell for a man, 50 years old,
# who smokes 15 cigarettes per day on average.
HT_mal(50, "male", 15, "Y")
```

`ht_mal_int` *Integrating hazard for the onset of th 1st malignant cell*

Description

Cumulative hazard for the onset of the first malignant cell between two time points (ages).

Usage

```
ht_mal_int(lower, upper, g, d, smoking)
```

Arguments

lower	age (years), lower limit of the integral
upper	age (years), upper limit of the integral
g	gender ("male", or "female")
d	smoking intensity group based on the average number of cigarettes smoked per day
smoking	binary variable indicating whether the person was smoking between ages "lower" and "upper" ("Y"=yes, "N"=no)

Details

Integration from age *'lower'* to age *'upper'* of the hazard rate h(t) for the onset of the first malignant cell, as described by the Two-Stage Clonal Expansion (TSCE) carcinogenesis model (see function 'HT_mal' for more details).

Value

The value of the calculated integral, equal to the probability of developing the first malignant cell between ages "lower" and "upper".

Author(s)

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References

Moolgavkar, S. H., and Luebeck, G. (1990) Two-event model for carcinogenesis: Biological, mathematical, and statistical considerations. *Risk Analysis*, 10(2):323-341.

Heidenreich, W. F., Luebeck, E. G. and Moolgavkar, S. H. (1997) Some properties of the hazard function of the two-mutation clonal expansion model. *Risk Analysis*, 17(3):391-399.

Hazelton, W. D., Clements, M. S. and Moolgavkar, S. H. (2005) Multistage carcinogenesis and lung cancer mortality in three cohorts. *Cancer Epidemiology Biomarkers & Prevention*, 14(5):1171-1181.

Hazelton, W. D., Luebeck, E. G., Heidenreich, W. E. and Moolgavkar, S. H.(2001) Analysis of a historical cohort of chinese tin miners with arsenic, radon, cigarette smoke, and pipe smoke exposures using the biologically based two-stage clonal expansion model. *Radiation Research*, 156(1):78-94.

Meza, R., Hazelton, W. D., Colditz, G. A. and Moolgavkar, S. H. (2008) Analysis of lung cancer incidence in the nurses' health and the health professionals' follow-up studies using a multistage carcinogenesis model. *Cancer Causes & Control*, 19(3):317-328.

See Also

HT_mal, t_mal

Examples

```
# The following examples calculate the probability of a man, who on average smokes
# 30 cigarettes per day, to develop the first malignant cell:
ht_mal_int(0, 50, "male", 30, "Y") # before the age of 50
ht_mal_int(0, 75, "male", 30, "Y") # before the age of 75
ht_mal_int(45, 75, "male", 30, "Y") # between the ages of 45 and 75
```

---

nat_hist *Simulate one individual trajectory*

Description

Function to run the MILC model and predict a full lung cancer trajectory depending on the age, gender and smoking history of an individual (see MILC-package for more details).

Usage

```
nat_hist(dat, pred_yrs, gender, status, ts, tq, m, cdiagn, creg, cdist)
```

Arguments

dat	7-dimensional numeric vector, with the first 5 values being random numbers from Unif[0,1], required for the simulation, and the 6th and 7th value referring to the age (years) and smoking intensity (number of cigarettes) respectively.
pred_yrs	prediction period (years)
gender	"male" or "female"
status	smoking status, i.e., whether the person is "never", "former", or "current" smoker
ts	start smoking age (years), when relevant
tq	quit smoking age (years), when relevant
m	scale parameter of the Gompertz distribution assumed for the tumor growth
cdiagn	2-dimensional vector with location and scale parameters of the log-Normal distribution assumed for the tumor volume at diagnosis
creg	2-dimensional vector with location and scale parameters of the log-Normal distribution assumed for the tumor volume at the beginning of the regional stage
cdist	2-dimensional vector with location and scale parameters of the log-Normal distribution assumed for the tumor volume at the beginning of the distant stage

Value

An R-object of type "list" with the following 20 components:

[[1]]: T-entry: age(years) at the beginning of the prediction period

[[2]]: T_mal: age(years) at the onset of the first malignant cell

[[3]]: T_reg: age(years) at the beginning of the regional stage

[[4]]: T_dist: age(years) at the beginning of the distant stage

[[5]]: T_diagn: age(years) at diagnosis

[[6]]: D_diagn: tumor diameter at diagnosis

[[7]]: stage: tumor stage at diagnosis

[[8]]: T-pred: age(years) at the end of the prediction period

[[9]]: T_do: predicted age(years) at death from a cause other than lung cancer

[[10]]: T_dl: predicted age(years) at death from lung cancer

[[11]]: T_final: age (years) at the end of the simulated trajectory

[[12]]: lung_inc: whether the person developed (1="Yes") lung cancer or not (0="No")

[[13]]: excl: exclude unreasonable cases ("Yes", "No")

[[14]]: cause: cause of death ("lung", "other", NA)

[[15]]: T_death: age(years) at death from any cause

[[16]]: gender

[[17]]: smoking status

[[18]]: start smoking age(years)

[[19]]: quit smoking age(years)

[[20]]: smoking intensity (number of cigarettes)

Author(s)

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See Also

t_mal, t_prog, tdeath_other, tdeath_lung

Examples

```
# In the following examples we predict lung cancer trajectories for a man, 50 years old
# at the beginning of the prediction period, who has started smoking at the age of 20 years
# and smokes 30 cigerettes per day on average. The model predicts 20 years ahead.

# We present three possible trajectories:

# In the first case the person does not die before the end of the prediction period:
set.seed(33)
nat_hist ( c(runif(5),50,30), 20, "male", "current", 20, NA,
0.00042, c(3.91, 3.91), c(1.1, 1.1), c(2.8, 2.8))

# In the second case the person dies at the age of 62.43 years from lung cancer:
set.seed(1470)
nat_hist ( c(runif(5),50,30), 20, "male", "current", 20, NA,
0.00042, c(3.91, 3.91), c(1.1, 1.1), c(2.8, 2.8))

# In the third case the person dies at the age of 69.68 years from a cause
```

```
# other than lung cancer:
set.seed(1450)
nat_hist ( c(runif(5),50,30), 20, "male", "current", 20, NA,
0.00042, c(3.91, 3.91), c(1.1, 1.1), c(2.8, 2.8))
```

---

never.other *never.other dataset*

Description

An R object of class "list" containing Cumulative Incidence Function estimates for other cause (not lung cancer) mortality, for non smokers by age (5-years age group), and gender ("male" or "female").

Usage

```
never.other
```

Format

The *'never.other'* list comprises 22 components in total. Each component itself is an R object of class "list" with three components, i.e.:

[[1]] a vector with time points (in years)

[[2]] a vector with CIF estimates

[[3]] a vector with variances of the CIF estimates

Source

CIF estimates are derived using data obtained from the National Health Interview Survey (NHIS) database covering the years 1986-2004.

See Also

ci.lung, current.other, former.other

Examples

```
data(never.other)
never.other[1]
never.other[[1]][1] # time (years)
never.other[[1]][2] # CIF estimates
never.other[[1]][3] # variances of CIF estimates
```

`tdeath_lung` *Predict the age at death from lung cancer*

Description

Function to predict the age (years) at which a person may die of lung cancer given gender, age and tumor stage at diagnosis.

Usage

```
tdeath_lung(u1, u2, covs_lung)
```

Arguments

`u1, u2`	random numbers from Unif[0,1] required for the simulation
`covs_lung`	3-dimensional vector with values for the covariates related to death from lung cancer, i.e., tumor stage at diagnosis ("localized", "regional", or "distant"), age (years) at diagnosis, and gender ("male" or "female")

Value

An R-object of class "list" with the following six components:

[[1]]: random number u1 used in the simulation

[[2]]: random number u2 used in the simulation

[[3]]: index number of the time interval

[[4]]: age (years) at death from lung cancer

[[5]]: whether the person died of lung cancer("Yes") or not("No")

[[6]]: R-object of class "list" with the relevant CIF estimates

Note

Components [[1]]-[[3]] and [[6]] are returned for testing purposes only.

Author(s)

Stavroula A. Chrysanthopoulou

See Also

`ci.lung`, `tdeath_other`

Examples

```
# Predict the age at death from lung cancer for a woman, diagnosed with
# "localized" tumor at the age of 89 years
data(ci.lung)
d.lung <- tdeath_lung(runif(1), runif(1), c("localized", 89, "female"))
d.lung[[1]]
d.lung[[2]]
d.lung[[3]]
d.lung[[4]]
d.lung[[5]]
d.lung[[6]]
```

---

tdeath_other *Predict the age at death from a cause other than lung cancer*

Description

Function to predict the age (years) at which a person may die from a cause other than lung cancer given age, gender and smoking intensity, when relevant.

Usage

```
tdeath_other(u1, u2, status, covs_other)
```

Arguments

u1, u2	random numbers from Unif[0,1] required for the simulation
status	smoking status ("never", "former", or "current" smoker)
covs_other	3-dimensional vector with values for the covariates (other than smoking status) related to death from other causes, i.e., age (years) at the beginning of the prediction period, gender, smoking intensity expressed as average number of cigarettes smoked per day.

Value

An R-object of class "list" with the following six components:

[[1]]: random number u1 used in the simulation

[[2]]: random number u2 used in the simulation

[[3]]: index number of the time interval

[[4]]: time interval at which death from other causes may occur

[[5]]: age (years) at death from cause other than lung cancer

[[6]]: R-object of class "list" with the relevant CIF estimates

Note

Components [[1]]-[[4]] and [[6]] are returned for testing purposes only.

Author(s)

Stavroula A. Chrysanthopoulou

See Also

current.other, former.other, never.other, tdeath_lung

Examples

```
# Predict the age at death from a cause other than lung cancer for a man 52 years old,
# who have never smoked.
data(current.other, former.other, never.other)
d.other <- tdeath_other(runif(1), runif(1), "never", c(52, "male", NA))
d.other[[1]]
d.other[[2]]
d.other[[3]]
d.other[[4]]
d.other[[5]]
d.other[[6]]
```

---

t_mal *Predict age at the onset of the first malignant cell*

Description

Function to predict the age at the onset of the first malignant given gender and smoking history, when relevant.

Usage

```
t_mal(u, g, ts, tq, d)
```

Arguments

u	random number required for the prediction
g	gender ("male" or "female")
ts	start smoking age (years)
tq	quit smoking age (years)
d	smoking intensity expressed as average number of cigarettes smoked per day

Details

The age at the onset for the first malignant cell is simulated based on the relevant hazard h(t) described by the TSCE carcinogenesis model (see function 'HT_mal' for more details). Smoking history includes start and quit smoking ages, and smoking intensity expressed as average number of cigarettes smoked per day.

Value

Predicted age (years) at which a person may develop the first malignant cell.

Author(s)

Stavroula A. Chrysanthopoulou

References

Moolgavkar, S. H., and Luebeck, G. (1990) Two-event model for carcinogenesis: Biological, mathematical, and statistical considerations. *Risk Analysis*, 10(2):323-341.

Heidenreich, W. F., Luebeck, E. G. and Moolgavkar, S. H. (1997) Some properties of the hazard function of the two-mutation clonal expansion model. *Risk Analysis*, 17(3):391-399.

Hazelton, W. D., Clements, M. S. and Moolgavkar, S. H. (2005) Multistage carcinogenesis and lung cancer mortality in three cohorts. *Cancer Epidemiology Biomarkers & Prevention*, 14(5):1171-1181.

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Meza, R., Hazelton, W. D., Colditz, G. A. and Moolgavkar, S. H. (2008) Analysis of lung cancer incidence in the nurses' health and the health professionals' follow-up studies using a multistage carcinogenesis model. *Cancer Causes & Control*, 19(3):317-328.

See Also

HT_mal, ht_mal_int, nat_hist

Examples

```
# The following examples predict the possible ages at the onset of the first
# malignant cell of:

set.seed(7461)
# a man who has never smoked:
   t_mal(runif(1), "male", NA, NA, NA)

# a man, current smoker,who started smoking at 20 years:
   t_mal(runif(1), "male", 20, NA, 25)

# a man, former smoker, who started and quit smoking at 20 and 50 years respectively,
# and used to smoke 25 cigarettes per day on average:
   t_mal(runif(1), "male", 20, 50, 25)
```

t_prog *Predict age at distinct lung cancer natural history stages*

Description

Function to simulate the time points (years) from the onset of the first malignant cell to major states in the natural history of lung cancer, i.e., the time at the beginning of the regional (Treg), and distant (Tdist) stage, and time at diagnosis (Tdiagn).

Usage

```
t_prog(N, m, cdiagn, creg, cdist)
```

Arguments

N	Total number of random numbers from the log-Normal distributions
m	scale parameter of the Gompertz distribution for the tumor growth
cdiagn	vector with location and scale parameters for the logNormal distribution of the tumor volume at diagnosis.
creg	vector with location and scale parameters for the logNormal distribution of the tumor volume at the beginning of the regional stage.
cdist	vector with location and scale parameters for the logNormal distribution of the tumor volume at the beginning of the distant stage.

Details

The MILC model employs the Gompertz function to describe the tumor growth, i.e., the tumor volume V(t) at age t is:

$$\frac{V(t)}{V_0} = e^{\frac{s}{m}(1-e^{-mt})}$$

where, V_0 is the minimum tumor volume (one malignant cell), and m, s are the scale and shape parameters of the Gompertz distribution. Assuming a spherical tumor growth, the tumor size as a function of its diameter d(t) at age t, is:

$$V(t) = \frac{\pi}{6}[d(t)]^3$$

.

Given a Gompertzian tumor growth, the distribution of tumor volumes at specific time points can be described by a log-Normal distribution, having as starting point the beginning of the local stage (onset of the first malignant cell). We define three different log-Normal distributions to simulate the tumor volume at the beginning of the regional (V_{reg}), and distant stage (V_{dist}), as well as the tumor at diagnosis (V_{diagn}).

Value

An R-object of class "list" with the following five components:

[[1]] T_reg: time(years) from the onset of the first malignant cell to the beginning of the regional tumor stage

[[2]] T_dist: time(years) from the onset of the first malignant cell to the beginning of the distant tumor stage

[[3]] T_diagn: time(years) from the onset of the first malignant cell to diagnosis

[[4]] D_diagn: tumor diameter at diagnosis

[[5]] stage: tumor stage at diagnosis

Author(s)

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References

Detterbeck, F. C. and Gibson, C. J. (2008) Turning gray: The natural history of lung cancer over time. *Journal of Thoracic Oncology*, 3(7):781-792.

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See Also

t_vol

Examples

```
# Predicted disease progression given certain values of the log-normal and Gompertz
# distributions assumed for the tumor volumes and growth in the MILC model.
 t_prog (1, 0.00042, c(3.91, 3.91), c(1.1, 1.1), c(2.8, 2.8))
```

t_vol *Predict age at given tumor volume*

Description

Function to predict the time (years) at which tumor has reached volume V from the onset of the first malignant cell.

Usage

```
t_vol(vol, m)
```

Arguments

vol	tumor volume (mm^3)
m	scale parameter of the Gompertz distribution assumed for the tumor growth

Value

Time (years) from the onset of the first malignant cell at which tumor reaches volume 'vol'.

Author(s)

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References

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Laird, A. K. (1964) Dynamics of tumor growth. *British Journal of Cancer*, 18(3):490-502.

See Also

t_prog

Examples

```
# Time (years) elapsed from the onset of the first malignant cell until
# the tumor reaches volume:

# 0.5 mm^3:
t_vol(0.5, 0.00042)


# 10 mm^3:
t_vol(10, 0.00042)
```

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